CHAPTER-1

INTRODUCTION
1.0 INTRODUCTION

Gabapentin is described as 1-(aminomethyl-1-cyclohexyl) acetic acid, a non-metabolized antiepileptic compound, developed as a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA) that crosses the blood-brain barrier. Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years. Gabapentin is also indicated for the management of postherpetic neuralgia. It also used to treat partial seizures in paediatric patients and neuropathic pain in adults.

The mechanism of action by which Gabapentin is exerting its anticonvulsant and analgesic activities are not completely understood. More recently the alpha-2-delta-1 subunit of the voltage-dependent calcium channels have been identified as a binding target and produce pharmacological activity of antiepileptic, analgesic and anxiolytic properties in animal studies. The most commonly observed adverse events associated with the use of gabapentin in adults are dizziness, somnolence and peripheral edema. It is available in tablets, capsules, or oral solution forms.

All pharmacological actions following Gabapentin administration are due to the activity of the parent compound. Gabapentin is not appreciably metabolized in humans and its oral bioavailability is not fully linear over the entire therapeutic range. Gastrointestinal tract absorption occurs via the L-amino acid saturable transport system in the proximal small bowel, which is responsible for the lack of dose proportionality for higher doses. Food has only a slight effect on the rate and the extent of absorption of Gabapentin (14 % increase in AUC and Cmax). Less than 3 % of Gabapentin circulates bound to plasma protein. Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Its elimination half-life is 5 to 7 hours and unaltered by dose or following multiple dosing. Plasma levels of 2-20 mg/ml are shown in various clinical trial studies. It is not necessary to monitor the Gabapentin plasma concentration to optimize therapy since it is not an enzyme inducer or an inhibitor or does not alter the co-administered anticonvulsant. It is meant to say that it is not a narrow therapeutic index drug but is a low variable drug. It is a BCS Class
3 drug of high solubility and low permeability category. The FDA classified it as an AB rated
drug, having actual or potential bioequivalence issues. The drug has been proven to meet the
necessary bioequivalence requirements through in vivo testing compared to a reference
standard that is currently approved.

Neurontin, the global innovator drug of Gabapenton (solid dosage form) was launched by the
Pfizer Company, approved for partial seizure in 1993 by the FDA and marketed in the USA.
In 2004, the patent period for Neurontin expired. Pfizer produced its own generic form along
with other pharmaceutical companies in the USA and launched its product in India in the
year 2000. In India, Sun Pharma and Intas Pharma launched Gabapentin (generic to
Neurontin) formulation in the year 1998. At present, Neurontin is unavailable in Indian
market and the reason is unknown. Therefore, in global perspective, India is exposed to only
generic drug formulations of Gabapentin.

Generic drug products need to conform to the same standards of quality, efficacy and safety
as that of the innovator product. In addition, reasonable assurance must be provided that they
are, as intended, clinically interchangeable and nominally equivalent to innovator product.
But many developing countries do not have an effective means of monitoring the quality of
generic drug products in the market and many small scale industries and even some large
scale pharmaceutical companies are not compliant to GMP, GLP, GCP and Drug Regulation.
This results in widespread distribution of substandard and/or counterfeit drug products in the
market. Therefore, the lack of bioequivalence among different brands has been well
documented with digoxin, phenobarbital, prednisolone, tolbutamide, diclofenac sodium and
aspirin\textsuperscript{9-14}.

Generally full authority is granted to pharmacists to switch between different generic
versions of the innovator product because all generic products are proven bioequivalent to
innovator drug. It is assumed that generic products are freely interchangeable. However, no
data are available to suggest that this theme is tenable\textsuperscript{15}. Interestingly, the FDA does not
specify that a generic drug product can be substituted by another generic product, even
though these generic products have demonstrated bioequivalent to the innovator product\textsuperscript{16}. Thus, concerns arise when the concept of substitution is adopted.

In clinical practice, if there are multiple generic manufacturers for a drug, it is possible for patients to receive a different generic formulation each time they present a prescription. When patient switches between different generic formulations, there is potential for greater variation in drug pharmacokinetics than generic to innovator substitution. It is theoretically possible for average patients to experience an almost 50\% increase in serum concentrations if switched from a low BA generic formulation to high BA generic formulation. Conversely, the average patients could have an almost 33\% decrease in serum concentration if switched from high BA to low BA generic formulations\textsuperscript{17}. In another report it was disclosed that the mean AUC and Cmax may differ by 45\% in more extreme cases (i.e. 80\% generics versus 125\% generics) and that the generic to generic switch is more dangerous than innovator to generic switch which leads to a significant proposition of patients being exposed to problem in therapeutic equivalence, especially the safety concern\textsuperscript{18}.

For therapeutic equivalence the generic companies may file ANDA submission to the regulatory authority for generic approval. For each submission, the primary objective is to demonstrate that the generic formulation is bioequivalent of the innovator drug. It is of no interest to the generic drug company to show that its generic drug product is bioequivalent to other generic drug products made by other generic companies. On the other hand, if there are a number of submissions for the same innovator drug product, it would be a concern to the FDA whether these copies of the same innovator drug would be bioequivalent to one another. As a result, comparing bioavailability among generic copies of the same innovator drug which can be used as a safety monitoring tool for generic drug products is of interest to the regulatory authority.

The therapeutic equivalence in variation among generic products is because of the difference in manufacturing methodology and ANDA approval procedure. The generic drug is compared with the reference drug for ANDA approval. Sometimes the reference drug is not uniform in its availability and quality. There may be many post approval modifications in the
Chapter 1

Introduction

formulation. For public information the USFDA is maintaining the Orange Book\textsuperscript{19} which includes the Reference Listed Drug (RLD) status and the generic drugs which are proven for therapeutic equivalence to RLD. This information is available online and shows the transparency in ANDA approval process in the USA. This gives provision of immediate switch to available generic products which are equivalent to RLD by healthcare provider when required by the patients. In India, the reference product is called as a Designated Reference Product (DRP) in ANDA approval and normally it is a global innovator product. In case of its unavailability, one of the available generic products will be decided as a DRP by the Regulatory Authority\textsuperscript{20}. The information about the name of the DRP and therapeutic equivalence of generic products to DRP is not freely available to public. The generic drugs are approved on the basis of the reference drug. The generic products available in the market are more variable in therapeutic equivalence if the status of the reference drug itself is changing in availability, quality status and purity form with change of time.

A review about 2070 bioequivalence studies found that the average difference in Cmax and AUC between generic and innovator products was 4.35% and 3.56% respectively\textsuperscript{21}. The generic product AUC differed from the innovator product by less than 5% according to the bioequivalent method of the FDA guideline which is ideal for the approved formulation and more than 10% difference will pass the bioequivalent limit which is very rare. From this, Anderson and Hauck said that the generic product are known to change only 5-10% in average exposure\textsuperscript{22} which is extrapolating less than 5% into 10% in mean exposure. The variation is high among the available marketed formulations due to the malpractice of manufacturers and may possibly show the problem in therapeutic equivalence when these products are substituted with each other. The patient’s safety may be compromised. The patient’s safety is extremely compromised if it is associated with certain disease condition and drug properties. Similarly certain available formulations are not interchangeable in clinical practice due to a problem in therapeutic equivalence e.g. Carbamazepine, Phenytoin and Sodium volproate\textsuperscript{23}. In case with the carbamazipine use, switching from one generic to another generic at the same dose level could produce changes in AUC by as much as 21% and variations of the Cmax of up to 40% which can have the potential for significant shifts in circulating drug concentration in patients. Therefore switching from one generic product to
another can produce swings in concentration that can exceed the bioequivalent limit established by the FDA$^{24}$.

Every country will have their own control about the safe substitution of the innovator/reference drug with generic formulations through ANDA approval to encourage the use of generic drugs at the market. Many countries do not have effective means of monitoring the quality of generic and innovator/reference drug in the market. Many small scale industries and even some large scale pharmaceutical companies are not in compliance with GMP, GLP, GCP and Drug Regulation. This results in widespread distribution of substandard drug products in the market. The comparisons between different generic formulations are rare$^{17, 18,}$ and $^{24}$ If it is compared, it focuses on its own hospital policy for prescription written within optimal healthcare, company policy for no interest and pharmacy policy for purchasing and dispensing of the medicine with reasonable price. The comparisons in terms of quality are renewable periodically and remain unpublished in any journal. The patient is unaware about the complexity of generic substitution and the physician is also unaware about the issues in generic drug use pattern whether the substitution is safe or not. The scope for appropriate drug therapy with reasonable health care budget using generic drugs is lost.

Therefore, this study was focused on the drug interchangeability of three generic formulations available in the market which ultimately helps to achieve the appropriate drug therapy in clinical practice and health care provider with reasonable health care budget.