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Scope of the study: Gabapentin, the global innovator drug Neurontin (solid dosage form) was launched by Pfizer. It was approved for partial seizures in 1993 by the FDA and marketed in the USA. In 2004 patent periods for Neurontin expired. Pfizer produced its own generic form along with other pharmaceutical companies in the USA and it 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. Currently, Neurontin innovator product of Gabapentin is unavailable in Indian market and the reason is unknown. Therefore, in global perspective India is exposed to only generic drug formulations of Gabapentin available in the market.

Generally full impunity is granted to pharmacists to switch between different generic versions of 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. 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 bioequivalence to the same innovator product. 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 the average patients to experience an almost 50% increase in serum concentrations if switched from a low BA generic formulation to high BA generic formulations. Conversely, the average patients could have an almost 33% decrease in serum concentration if switched from high BA to low BA generic formulations. In another report it was reported 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.

The therapeutic equivalence is more variable among generic products because of 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 all over the world. There may be many post approval modifications in the formulation. For public information the USFDA is maintaining the Orange Book 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 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 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. 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 reference drug. The generic products, available in the market place are more variable in therapeutic equivalence if the status of reference drug itself is changing the availability, quality status and purity form with change of time.

Every country will have their own control about the safe substitution of innovator/reference drug with generic formulations through ANDA approval to encourage the use of generic drugs at the market place. 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. If it is compared, it is focused 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
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renewable periodically and remain unpublished in any journal. The patient is unaware of complexity of generic substitution and the physician is also unaware about the issues in generic drug use pattern and whether the substitution is safe or not. The scope for appropriate drug therapy with reasonable health budget using generic drugs is lost.

Therefore, the present 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 healthcare provider with reasonable health care budget.

Aim of the study:

Primary Objective

1. To compare the single dose oral bioavailability to determine the bioequivalence of three marketed generic Gabapentin 300 mg immediate release oral capsule formulations.

Secondary objective

2. In-vitro dissolution testing of three marketed generic products of Gabapentin 300 mg immediate release oral capsule formulations as per applicable pharmacopoeia standards.

3. To determine the drug interchangeability between three generic formulations based on bioequivalence status and dissolution properties.

The following three marketed formulations were evaluated

Product A: Gabalept ® 300 mg capsule, containing 300 mg of Gabapentin, manufactured by Micro Labs Ltd, Hosur - 635126, India.
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Product B: Gabantin® 300 mg capsule, containing 300 mg of Gabapentin, manufactured by Sun Pharmaceutical Industries, Dadra – 396191 or Kartholi, Jammu - 181133, India

Product C: Gabata® 300 mg capsule, containing 300 mg of Gabapentin, manufactured by Alkem Laboratories Ltd, Village-Thanha, Baddi, Himachal Pradesh – 173205, India

Note: For comparison purpose, Product A and Product C are considered as Test products and Product B was chosen as a Comparator reference product as per the following reasons
1. It is first launched in the India market along with the Intas Pharma.
2. Currently available in the US market and proven for therapeutic equivalency to the global innovator product and this information is freely available for public use through electronic Orange Book.
3. It can be considered as a comparator product as per the WHO guidelines of Generic drug approval process as approved by ICH region countries but the formulation is not perched from that country.

Methodology

1. In-vivo method (BA/BE study)

Study design: The study was conducted as an open label, balanced, randomized, three-treatment, three-period, three-sequence single-dose, crossover oral bioavailability study in 18 healthy adult, male, human subjects, under fasting conditions, comparing the bioequivalence of the two test products (A & C) with the comparator reference product (B). Each subject received one 300 mg Gabapentin capsule formulation with 240 ml of drinking water at ambient temperature after an overnight fast during each period. The order of receiving the different treatments for each subject during the three periods of the study was determined according to SAS generated randomization schedule.
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Ethical considerations: The study conducted at Ranbaxy Clinical Pharmacology Unit (Majeedia Hospital, New Delhi) after protocol approval by the Jamia Hamdard Institutional Review Board. Study was conducted according to ICH (62FR 25692, 09 May 1997) 'Guidance for Good Clinical Practice' guidelines and the principles enunciated in the Declaration of Helsinki (2004). All the subjects were fully informed and understood the study procedure. They provided written informed consent before entering into the study.

Study subjects: Eighteen healthy, adult, male, human subjects participated in the study. The mean±SD (range) of age, height and weight of the subjects were 28.22±7.30 years (20-40 years), 166.83±4.03 cm (159-171 cm) and 68.17±6.55 kg (49-71 kg) respectively. The mean±SD (range) of BMI was 20.90±2.30 kg/m² (17.78-24.98 kg/m²). All subjects were in good health as evidenced by the medical histories, complete physical examination and routine laboratory tests performed within 28 days prior to the enrollment of subjects in the study. None had a history of any allergy to Gabapentin and related compounds and experience of any symptoms/disease/adverse effects of Gabapentin as well. Subjects were selected according to inclusion and exclusion criteria as well. Subjects did not receive any medication during the period of two weeks prior to the start of the study. They were instructed during screening not to take any prescription and OTC medications subsequently until the completion of the study. All the subjects abstained from any xanthine-containing food or beverages or alcoholic products for 48 h prior to dosing and throughout the sampling schedule during each period. Subjects with a history of drug or alcohol abuse or drug sensitivity were excluded. Subjects were admitted and housed in the Clinical Pharmacology Unit from 12 h before the dose and were discharged 24 h after dose during each period. Two samples were collected as ambulatory sample on each period.

Sampling Schedule: A total of 57 blood samples (4 ml each) were collected from each subject. These consisted of 19 samples of pre-dose in duplicate and at 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 h post-dose. Samples were collected through an indwelling cannula placed in a forearm vein during each period. The collected blood samples were centrifuged at 2-8°C to separate the plasma. The separated plasma samples were stored at -70°C until analysis.
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Bioanalytical method: High-pressure liquid chromatography (HPLC), combined Mass Spectrometric (MS) procedure such as LC-MS/MS procedure performed for the quantitative determination of Gabapentin in the plasma. The sample preparation process was accomplished by solid phase extraction technique using extraction cartridge OASIS® MCX 1cc (30 mg) in acidic condition with hydrochloric acid. Then the Gabapentin is eluted from the cartridge by alkali condition with liquid ammonia solution. The evaporated ammonia solution is dried and reconstituted with mobile phase which is 20:80 ratio of acetonitrile and 10mM ammonium acetate buffer pH 6.6. Then the reconstituted solution is run in HPLC system which consists of Hypersil Hypurity Advance C18 column (25 cm X 4.6 mm ID) with a particle size of 5 µm with flow rate of 0.6 mL/min mobile phase. Mass Spectrometry was used as a detector and Gabapentin is quantified according to the mass to charge ratio of 172.1 m/z (parent) and 137.2 m/z (product) of Gabapentin. Signals from the detector were captured in a computer, and processed by using Analyst Software version 1.4.1 which is also used for data recording and processing. The assay was found to be selective, accurate and precise with linearity from 34.7 to 6943.1 ng/mL concentrations.

Pharmacokinetic analysis: The pharmacokinetic parameters were calculated using WinNonlin software Version 5.0.1. Cmax calculated as the maximum measured the plasma concentration over the time span specified and T\text{max} was calculated as the time of the maximum measured plasma concentration. Terminal elimination rate constant (Kel) was estimated from a semi-log plot of the plasma concentration versus time curve and calculated by linear least square regression analysis using the last three (or more) non-zero plasma concentrations. The terminal half-life (\text{t}_{1/2}) was calculated by the formula 0.693/Kel. The area under the plasma concentration versus time curve, from time zero to the last measurable concentration (\text{AUC}_{0\text{,t}}) was calculated by the linear trapezoidal method. The area under the plasma concentration versus time curve from the time zero to infinity (\text{AUC}_{0\text{,\infty}}) calculated by the sum of the \text{AUC}_{0\text{,t}} plus the ratio of the last measurable concentration on the elimination rate constant.
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Statistical analysis: Statistical analyses were carried out using SAS software version 9.1.3 (SAS Institute Inc. Cary NC, USA). The analysis includes the data of 18 subjects who had completed the study.

The Descriptive statistics i.e. Arithmetic mean, standard deviation, coefficient of variation were calculated for all pharmacokinetics parameters and geometric mean and percentage coefficient of variation of geometric means was calculated for AUC₀₋₄₅, AUC₀₋₇₅ and Cₘₐₓ.

The log-transformed pharmacokinetic parameters (Cₘₐₓ, AUC₀₋₄₅ and AUC₀₋₇₅) for Gabapentin were analyzed using a mixed effect ANOVA model using Type III sum of squares, with the main effects of sequence, period and formulations as fixed effects and subjects nested within the sequence as a random effect. A separate ANOVA model was used to analyze each of the parameters. The sequence effect was tested at the 0.10 level of significance using the subjects nested within sequence mean square as the error term. Treatment and period effects were tested at the 0.05 level of significance against the residual error (mean square error) from the ANOVA model as the error term. Each analysis of variance included calculation of least-squares means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analysis was done using the PROC GLM, SAS procedure.

The percentage point estimate (ratio of the least square means) for the log transformed pharmacokinetic parameters Cₘₐₓ, AUC₀₋₄₅ and AUC₀₋₇₅ were reported. The 90% CI of Cₘₐₓ, AUC₀₋₄₅ and AUC₀₋₇₅, for the ratio of test and comparative reference product was calculated by first calculating the 90% CI for the difference in the averages (arithmetic means) of the log (natural) transformed data and then taking antilog of the obtained confidence limits to assess bioequivalence using 90% CI of 80 – 125%.

2. In-vitro method (Dissolution Test)

The in-vitro dissolution method was carried out according to the USP Monograph 32 (2009) 11 using paddle type (Apparatus 2) with 50 rpm. The dissolution medium is 0.06N
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hydrochloric acid of 900 mL volumes and temperature set at 37°C ±0.5°C. The samples were withdrawn in 5, 10, 15, 20 and 30 minute intervals and they were analyzed by HPLC method with UV detection at 210-nm and the chromatographic separation was achieved using 4.6 mm x 25-cm column that contains 5-μm packing L7 and mobile phase which is a ratio of 940:60 mL of monobasic potassium phosphate of pH 6.9 and acetonitrile with 1.2 mL/min flow rate. The pH adjusted with 5N potassium hydroxide solution. The injection volume is 100 μL. The condition for passing the dissolution is not less than 80% of the labelled amount of Gabapentin should have dissolved in 20 minutes.

Findings: All the 18 subjects completed the study and no adverse event reported in the study. The summary statistical results indicate that the two marketed products A and C when compared to third marketed reference product of Gabapentin B, 90% CI falls within the bioequivalence limits of 80 – 125%. Thus, indicating a comparable rate and extent of absorption of all three marketed products of Gabapentin. The study achieved no formulation effect, period effect and sequence effect from the ANOVA result. The power was achieved above 80% in this study.

All the three products passed the USP standard dissolution test i.e. more than 80% of drug released within 20 minutes of dissolution time. The dissolution comparison shows that all the three products have very rapid dissolution properties i.e. More than 85% drug released within 15 minutes dissolution time. Therefore Product A, B and C are similar in passing the in-vitro test which is a surrogate for in-vivo bioequivalence. In this study, the In-vitro result is not shown major difference in the dissolution properties and the same was observed in the in-vivo result. The in-vivo results thus observed confirms the in vitro results to predict drug interchangeability.

Applications: The pharmaceutical products that are therapeutically equivalent are interchangeable in clinical practice. The therapeutic equivalence can be assured when the product both pharmaceutical equivalent/alternative and bioequivalent. The drug interchangeability also includes the equivalence of dosage forms as well as the indications and instructions for their use. In-view of this each product is the pharmaceutical equivalent
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and similar in dosage forms, indications and instructions for their use as well according to the label. The study also shows that the two marketed products of Gabapentin A and C when compared to third marketed product used as a reference product, prove bioequivalence. Therefore, the product A and C are therapeutically equivalent to product B and interchangeable in clinical practice for cost saving and availability of formulation in the pharmacy.

The safe interchangeability of therapeutically equivalent products of Gabapentin in clinical practice consists of two categories, one is nerve pain management and another is seizure control. There were no reported issues in brand substitution for Gabapentin use in nerve pain management. Whenever necessary, the change in low cost therapeutically equivalent generic product may be advisable which offer a substantial advantage in terms of cost saving. However with seizure control therapy, the cheaper therapeutically equivalent generic products are safely interchangeable with following instructions due to disease properties: At the time when treatment is initiated cheaper one should be preferred. When substitution of therapeutically equivalent generic product is necessary, it is desirable to carefully inform the patient and his/her healthcare provider about the nature and characteristics of these products and the regulations that govern their presence in the market. This is important to improve compliance and to relieve the anxiety that may be associated with receiving a prescription of these generic products. In patients already treated with an innovator product who have incomplete seizure control, it may be rational to switch to another drug; whenever change of product is necessary, careful patient monitoring is needed. However no Therapeutic Drug Monitoring (TDM) necessary in case of Gabapentin; in patients who achieved complete seizure remission, switching even therapeutic equivalent pharmaceutical products is not advisable unless otherwise any specific reasons like cost saving and drug availability at the market.

The change of a product A to B in clinical practice will save Rs.2.50/capsule. It will save the Minimum Accusation Cost (MAC) of Rs.7.50 daily and Rs.2737.50 annually to the patients according to clinical dose. Similarly, product B to C will save Rs. 2.00/capsule and it saves the MAC of Rs.6.00 daily and Rs.2190.00 annually. However the interchangeability of product
C with A was not included in the study due to difficulty in choosing the status of reference product which complies standard of medicine. The cheap one will save Rs 5.50/capsule and it saves the MAC of Rs.16.50 daily and Rs.6022.50 annually.