*Pharmacophore* 2014, Vol. 5 (2), 287-300 USA CODEN: PHARM7 ISSN 2229-5402

**Pharmacophore**

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

# BIOEQUIVALENCE STUDY OF ANTIMIGRAINE DRUG IN HEALTHY ADULT HUMAN SUBJECTS UNDER FED CONDITIONS

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## ABSTRACT

Bioequivalence studies are the preliminary requirement for generic products to enter in the market. International regulatory authorities require that the final quality judgment of an oral dosage form be based on its in vitro dissolution profile and its *in vivo* bioavailability or bioequivalence evaluation. This is an open label, balanced, randomized, two treatments, two periods, two sequences, single dose, cross-over, and bioequivalence study in (22) healthy, adult, subjects under fed conditions. Subjects was administered 20 ml of water before dosing, allowing to wet the mouth of the subject and then a single oral dose of test formulation Rizatriptan orally disintegrating tablets 10 mg or reference formulation Maxalt MLT® 10 mg (Rizatriptan benzoate) orally disintegrating tablets was placed on the tongue and allowed to disintegrate/ dissolve and swallowed with saliva under low light condition 30 min after initiation of a standardized high fat high calorie breakfast in period I. Similar procedure was followed in period II. Subjects received alternate treatments at the end of the study. The study was conducted according to the approved protocol, SOPs and ICH-GCP guidelines and applicable regulatory guidelines. A validated bio analytical method was adopted for conduct of analysis of the plasma samples of the study, which was selective, sensitive and cost effective. Based on geometric mean ratio of log transformed data and 90% confidence interval of test and reference product for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, it is concluded that the ratio and extent of absorption of test and reference product are similar.

**Keywords:** Bioequivalence study of 2 products, Anti-Migraine, Rizatriptan, Plasma concentration, Safety of volunteer's.

## INTRODUCTION

The spiraling health care expenditure are high priority area of concern for governments of most of countries in the world and governments are looking for rationalizing the expenditure and in optimizing health care. One way of the rationalization is the use, recommendations and introduction of generic drugs into the market as these produce immense saving to nation economy. Thus, they have to play an important role in holding down national spending on prescription drugs. Generics are of high significance in the countries where intellectual property laws are stringent. Once drug patent expire, monopoly of the innovator comes to end and generic drugs having the same formula as the brand-name drug are marketed at a much lower price. These drugs offer great advantage of being economical, as there is no significant change in the quality of the patient care and huge cost saving. Other advantages of generic drugs includes, more detailed information about the chemical composition and therapeutic applications.

- Use of uniform name for generic drug.
- Switch ability to a cheap drug in terms of quality and price.

Regulatory authorities Food and Drugs Administration (FDA) and European Medicines Agency (EMEA) insist that generic products should compulsorily be essential similar with that of reference product in order to exclude any clinically significant difference. The notion of essential similarity has three fundamental aspects. Comparing brand-name drug, the generic drug must have similar composition (same quality and type of active principle), route of administration and therapeutic equivalence (bioequivalence). Despite many advantages for consumers and health care providers, with low priced generic formulation, these are not always as safe or effective as their counterpart. Issue of impurities in manufacturing generic drugs had been addressed by US Office of generic drugs and draft guideline for industry has been proposed. Typically the migraine is unilateral (affecting one half of the head) and pulsating in nature, lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, photophobia (increased sensitivity to light), photophobia (increased sensitivity to sound) and the pain is generally aggravated by physical activity. Up to one-third of people with migraine headaches perceive an aura a transient visual, sensory, language, or motor disturbance which signals that the headache will soon occur. Occasionally an aura can occur with little or no headache following it.

Many important drugs like diclofenac sodium, theophylline, phenytoin, warfarin tablet, dioxin tablets and levothyroxine tablets have failed bioequivalence studies. Reports of the generic drugs having different in vitro profile in comparison to innovator product and substandard quality are frequent across many countries. Nevertheless, there has always been a report of variation in the efficacy of generic drugs compared with the corresponding brand name drugs. Thus, substitution in drug therapy can have significant effect on the risk benefit ratio in therapeutic situations where patient life is at risk. It is an important that cost saving in terms of generic should not be accrued at the expense of the quality of health care. Substitution of a brand name drug with a generic drug requires particular care from clinician side to ensure the safest and most effective treatment. It is an important concern for general practitioners who are mostly unaware of these unsatisfactory outcomes from generic substitution. There is thus a need for more detailed investigation of the potential consequences of changes from a brand name drug (switch ability, interchange ability and prescribe ability issues). Migraines are believed to be due to a mixture of environmental and genetic factors. About two-thirds of cases run in families. Fluctuating hormone levels may also play a role, as migraines affect slightly more boys than girls before puberty, but about two to three times more women than men. Propensity for migraines usually decreases during pregnancy. The exact mechanisms of migraine are not known. It is, however, believed to be a neurovascular disorder. The primary theory is related to increased excitability of the cerebral cortex and abnormal control of pain neurons in the trigeminal nucleus of the brainstem.

Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50%. Guidelines are fairly consistent in rating topiramate, divalproex, propranolol, and metoprolol as having the highest level of evidence for first-line use. Recommendations regarding effective-ness varied however for gabapentin. Timolol is also effective for migraine prevention and in reducing migraine attack frequency and severity, while frovatriptan is effective for prevention of menstrual migraine. Ami- triptyline and venlafaxine are probably also effective. Botox has been found to be useful in those with chronic migraines but not those with episodic ones, Triptans are a family of tryptamine-based drugs used as abortive medication in the treatment of migraines and cluster headaches. They were first introduced in the 1990s. While effective at treating individual headaches, they do not provide preventative treatment and are not considered a cure. Rizatriptan (trade name Maxalt) is a 5-HT1

agonist triptan drug developed for the treatment of migraine headaches. It is available in strengths of 5 and 10 mg as tablets and orally disintegrating tablets (Maxalt-MLT). Maxalt obtained approval by the United States Food and Drug Administration (FDA) on June 29, 1998. It is a second-generation triptan, MAXALT Wafer + Tablet.

## SIGNS & SYMPTOMS OF MIGRAINE

Migraines typically present with self-limited, recurrent severe headache associated with autonomic symptoms. About 15-30% of people with migraines experience migraines with an aura and those who have migraines with aura also frequently have migraines without aura. The severity of the pain, duration of the headache, and frequency of attacks is variable. A migraine lasting longer than 72 hours is termed status migrainosus. There are four possible phases to a migraine, although not all the phases are necessarily experienced (Bartleson, JD; 2010).

- The prodrome, which occurs hours or days before the headache
- The aura, which immediately precedes the headache
- The pain phase, also known as headache phase
- The postdrome, the effects experienced following the end of a migraine attack.

### Prodrome Phase

Prodarmal or premonitory symptoms occur in ~60% of those with migraines with an onset of two hours to two days before the start of pain or the aura. These symptoms may include a wide variety of phenomenon including altered mood irritability, depression etc, craving for certain food, stiff muscles (especially in the neck), constipation or diarrhea, and sensitivity to smells or noise. This may occur in those with either migraine with aura or migraine without aura.

### Aura Phase

An aura is a transient focal neurological phenomenon that occurs before or during the headache. They appear gradually over a number of minutes and generally last fewer than 60 minutes. Symptoms can be visual, sensory or motor in nature and many people experience more than one. Visual effects occur most frequently; they occur in up to 99% of cases and in more than 50% of cases are not accompanied by sensory or motor effects. Vision disturbances often consist of a scintillating scotoma (an area of partial alteration in the field of vision which flickers and may interfere with a person's ability to read or drive.) These typically start near the center of vision and then spread out to the sides with zigzagging lines which have been described as looking like fortifications or walls of a castle. Usually the lines are in black and white but some people also see colored lines. Some people lose part of their field of vision known as hemianopsia while others experience blurring. Sensory aurae are the second most common type; they occur in 30–40% of people with auras. Often a feeling of pins-and-needles begins on one side in the hand and arm and spreads to the nose-mouth area on the same side. Numbness usually occurs after the tingling has passed with a loss of position sense. Other symptoms of the aura phase can include: speech or language disturbances, world spinning, and less commonly motor problems. Motor symptoms indicate that this is a hemiplegic migraine, and weakness often lasts longer than one hour unlike other auras.

### Pain Phase

Classically the headache is unilateral, throbbing, and moderate to severe in intensity. It usually comes on gradually and is aggravated by physical activity. In more than 40% of cases however the pain may be bilateral, and neck pain is commonly associated. Bilateral pain is particularly common in those who have migraines without an aura. Less commonly pain may occur primarily in the back or top of the head. The pain usually lasts 4 to 72 hours in adults, however in young children frequently lasts less than 1 hour. The frequency of attacks is variable, from a few in a lifetime to several a weeks, with the average being about one a month. The pain is frequently accompanied by nausea, vomiting, sensitivity to light, sensitivity to sound, sensitive to smells, fatigue and irritability. In a basilar migraine, a migraine with neurological symptoms related to the brain stem or with

neurological symptoms on both sides of the body, common effects include: a sense of the world spinning, light-headedness, and confusion. Nausea occurs in almost 90% of people, and vomiting occurs in about one-third. Many thus seek a dark and quiet room. Other symptoms may include: blurred vision, nasal stuffiness, diarrhea, frequent urination, pallor, or sweating. Swelling or tenderness of the scalp may occur as can neck stiffness.

### Postdrome Phase

The effects of migraine may persist for some days after the main headache has ended; this is called the migraine postdrome. Many report a sore feeling in the area where the migraine was, and some report impaired thinking for a few days after the headache has passed. The patient may feel tired or "hung over" and have head pain, cognitive difficulties, gastrointestinal symptoms, mood changes, and weakness. According to one summary, "Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise.

## CAUSES OF MIGRAINE

The underlying causes of migraines are unknown. However, they are believed to be related to a mix of environmental and genetic factors. They run in families in about two-thirds of cases and rarely occur due to a single gene defect. While migraines were once believed to be more common in those of high intelligence, this does not appear to be true. A number of psychological conditions are associated including: depression, anxiety, and bipolar disorder as are many biological events or triggers.

### Genetics

Studies of twins indicate a 34% to 51% genetic influence of likelihood to develop migraine headaches. This genetic relationship is stronger for migraines with aura than for migraines without aura.

### Triggers

Migraines may be induced by triggers, with some reporting it as an influence in a minority of cases and others the majority. Many things have been labeled as triggers; however the strength and significance of these relationships are uncertain. A trigger may be encountered up to 24 hours prior to the onset of symptoms.

### Physiological Aspects

Common triggers quoted are stress, hunger, and fatigue (these equally contribute to tension headaches; Migraines are more likely to occur around menstruation. Other hormonal influences, such as menarche, oral contraceptive use, pregnancy, per menopause, and menopause, also play a role. These hormonal influences seem to play a greater role in migraine without aura. Migraines typically do not occur during the second and third trimesters or following menopause.

### Dietary Aspects

Reviews of dietary triggers have found that evidence mostly relies on self-reports and is not rigorous enough to prove or disprove any particular triggers. Regarding specific agents there does not appear to be evidence for an effect of tyramine on migraine and while monosodium glutamate (MSG) is frequently reported as dietary trigger evidence does not consistently support this.

### Environmental Aspects

A review on potential triggers in the indoor and outdoor environment concluded the overall evidence was of poor quality, but nevertheless suggested people with migraines take some preventive measures related to indoor air quality and lighting. (Schurks, M; 2012)

## DIAGNOSIS

The diagnosis of a migraine is based on signs and symptoms. Imaging tests are occasionally performed to exclude other causes of headaches. It is believed that a substantial number of people with the condition have not been diagnosed. The diagnosis of migraine without aura, according to the International Headache Society, can be made according to the following criteria, the “5, 4, 3, 2, 1 criteria”. Five or more attacks for migraine *with* aura, two attacks are sufficient for diagnosis.

Four hours to three days in duration

Two or more of the following:

Unilateral (affecting half the head)

Pulsating,

“Moderate or severe pain intensity”

"Aggravation by or causing avoidance of routine physical activity"

One or more of the following:

Nausea and/or vomiting. Sensitivity to both light (photophobia) and sound (phonophobia).

If someone experiences two of the following: photophobia, nausea, or inability to work / study for a day the diagnosis is more likely. In those with four out of five of the following: pulsating headache, duration of 4–72 hours, pain on one side of the head, nausea, or symptoms that interfere with the person's life, the probability that this is a migraine is 92%. In those with less than three of these symptoms the probability is 17%.

## PREVENTIONS

Preventive treatments of migraines include: medications, nutritional supplements, lifestyle alterations, and surgery. Prevention is recommended in those who have headaches more than two days a week, cannot tolerate the medications used to treat acute attacks, or those with severe attacks that are not easily controlled. The goal is to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of abortive therapy. Another reason for prevention is to avoid medication overuse headache. This is a common problem and can result in chronic daily headache.

## TREATMENT

### Medication

Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50%. Guidelines are fairly consistent in rating topiramate, divalproex, propranolol, and metoprolol as having the highest level of evidence for first-line use. Recommendations regarding effectiveness varied however for gabapentin. Timolol is also effective for migraine prevention and in reducing migraine attack frequency and severity, while frovatriptan is effective for prevention of menstrual migraine. Amitriptyline and venlafaxine are probably also effective. Botox has been found to be useful in those with chronic migraines but not those with episodic ones.

### Alternative Therapies

While acupuncture may be effective, "true" acupuncture is not more efficient than sham acupuncture, a practice where needles are placed randomly. Both have a possibility of being more effective than routine care, with fewer adverse effects than preventative medications. Chiropractic manipulation, physiotherapy, massage and relaxation might be as effective as propranolol or topiramate in the prevention of migraine headaches; however, the research had some problems with methodology. The evidence to support spinal__ is poor and manipulation, insufficient to support its use. .

### Devices and Surgery

Medical devices, such as biofeedback and neurostimulators, have some advantages in migraine prevention, mainly when common anti-migraine medications are contraindicated or in case of medication overuse. Biofeedback helps people be conscious of some physiological parameters so as to control them and try to relax and may be efficient for migraine treatment. Neurostimulation uses implantable neuro-stimulators similar to pacemakers for the treatment of intractable chronic migraines with encouraging results for severe cases. Migraine surgery, which involves decompression of certain nerves around the head and neck, may be an option in certain people who do not improve with medications.

### Management

### Analgesics

Recommended initial treatment for those with mild to moderate symptoms are simple analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) or the combination of paracetamol, acetylsalicylic acid, and caffeine. A number of NSAIDs have evidence to support their use. Ibuprofen has been found to provide effective pain relief in about half of people and diclofenac has been found effective. Aspirin can relieve moderate to severe migraine pain, with effectiveness similar to sumatriptan. Ketorolac is available in an intravenous formulation. Paracetamol (also known as acetaminophen), either alone or in combination with metoclopramide, is other effective treatment with a low risk of adverse effects in pregnancy,

paracetamol and metoclopramide are deemed safe as are NSAIDs until the third trimester.

### Triptans

Triptans such as sumatriptan are effective for both pain and nausea in up to 75% of people. They are the initially recommended treatments for those with moderate to severe pain or those with milder symptoms who do not respond to simple analgesics the different forms available include oral, injectable, nasal spray, and oral dissolving tablets. In general, all the triptans appear equally effective, with similar side effects.

## LIFESTYLE CHANGES

Lifestyle Changes Making a few minor changes in your lifestyle can make your migraines more bearable. Improving sleep habits is important for everyone, and especially those with headaches. What you eat also has a huge impact on migraines, so dietary changes can be extremely beneficial, too.

### Avoid Food Triggers

Avoiding foods that trigger migraine is an important preventive measure. Common food triggers include monosodium glutamate (MSG), processed lunch meats that contain nitrates, dried fruits that contain sulfites, aged cheese, alcohol and red wine, chocolate, and caffeine. However, people's responses to triggers differ. Keeping a headache diary that tracks diet and headache onset can help identify individual food triggers.

### Eat Regularly

Eating regularly is important to prevent low blood sugar. People with migraines who fast periodically for religious reasons might consider taking preventive medications.

### Stay Physically Active

Exercise is certainly helpful for relieving stress. An analysis of several studies reported that aerobic exercise in particular might help prevent migraines. It is important, however, to warm up gradually before beginning a session, since sudden, vigorous exercise might actually precipitate or aggravate a migraine attack.

## RIZATRIPTAN (TRIPTANS)

Triptans are a family of tryptamine-based drugs used as abortive medication in the treatment of migraines and cluster headaches. They were first introduced in the 1990s. While effective at treating individual headaches, they do not provide preventative treatment and are not considered a cure. Rizatriptan (trade name Maxalt) is a 5-HT1 agonist triptan drug developed for the treatment of migraine headaches. It is available in strengths of 5 and 10 mg as tablets and orally disintegrating tablets (Maxalt-MLT). Maxalt obtained approval by the United States Food and Drug Administration (FDA) on June 29, 1998. It is a second-generation triptan, MAXALT Wafer + Tablet.

## INCLUSION CRITERIA

- Literate male subjects in the age range of 18- 45 years (both inclusive).
- BMI range within 18.50- 24.99 kg/m2 (including both).
- Had voluntarily given written informed consent to participate in this study.
- Were of normal health as determined by medical history, physical examination and laboratory investigations of the subjects performed within 21 days prior to the commencement of the study.

Comprehension of the nature and the purpose of the study and the compliance with the requirement of the entire protocol.

## EXCLUSION CRITERIA

- Hypersensitivity or intolerance to Rizatriptan or related group of drugs.
- History of pancreatitis or hepatitis or gastritis or gastrointestinal ulcer/ bleeding.
- History of drug induced rash, anaphylaxis, and photosensitivity reaction.
- History of seizures.
- History of myocardial infarction.
- History of any psychiatric illness which may impair the ability to provide written informed consent.

- Any evidence of organ dysfunction or any clinically significant deviation from the normal, in physical or clinical determinations.
- Presence of disease markers of HIV 1 and 2, Hepatitis B and C viruses or syphilis infection.
- Laboratory values that are significantly different the normal reference range and/ or are deemed to be of clinical significance by the investigator. Positive for the breath alcohol test and/or urine drug screen (barbiturates, benzodiazepines, amphetamine, cocaine, opiates, tetra-hydro cannabinod).
- Clinically abnormal ECG or Chest X-ray.
- Systolic blood pressure less than 100 mm Hg or more than or equal to 140 mm Hg.
- Diastolic blood pressure less than 60 mm Hg or more than or equal to 90 mm Hg.
- Pulse rate less than 60 beats/ minute or more than equal to 100 beats / minute.
- Difficulty with donating blood.
- History of smoking (positive history of smoking from last one year).
- History of high caffeine.
- Use of any enzyme modifying drugs, MAOIs and other prescription drugs within 30 days prior to day 1 of the study or use of any other over the counter medications during the two weeks period prior to the onset of study.
- Participation in any clinical trial within 12 weeks preceding day 1 of this screening(Elimination half-life of the study drug will be taken into consideration for inclusion of the subject in the study).
- Subjects who, through completion of this study, would have donated and /or lost more than 500 mL of blood in the past 3 months.

## SAMPLE SIZE

A sample size of twenty two (22) healthy adult human subjects fulfilling the inclusion criteria. Plasma samples of all evaluated subjects completing both the periods of the study will be analyzed.

## RANDOMIZATION

Randomization schedule for all 22 volunteer was generated before the start of study by using SAS software. Volunteers were administered each treatment (Test or Reference). During the two period of the study according to the randomization schedule. The randomization was balanced and code was kept under controlled access. The drug accountability was maintained by pharmacist throughout study under supervision of chief investigator. All the study drugs (i.e. dispensed but un-dosed) returned from bio study was sent back to pharmacy and recorded.

No concomitant drug therapy was allowed during the study except one (S) used to an adverse event. Study personnel involved in the sample analysis was kept blinded from the randomization code till the completion of the bio-analytical phase of the study.

### Selection of Doses In The Study

The recommended standard dosage of Rizatriptan is 5 mg to 10 mg for acute treatment of migraine in adults. Hence, Rizatriptan orally disintegrating tablets 10 mg and the same was used in this study as test formulation and the corresponding reference formulation was selected accordingly.

## METHODOLOGY USED IN ADMINISTRATION OF DRUG

Subjects was administered 20 ml of water before dosing, allowing to wet the mouth of the subject and then a single oral dose of test formulation Rizatriptan orally disintegrating tablets 10 mg or reference formulation Maxalt MLT® 10 mg (Rizatriptan benzoate) orally disintegrating tablets was placed on the tongue and allowed to disintegrate/ dissolve and swallowed with saliva under low light condition 30 min after initiation of a standardized high fat high calorie breakfast in period I. similar procedure was followed in period II. Subjects received alternate treatments at the

end of the study. During the course of the study, safety parameters assessed were vital signs – oral temperature, sitting BP and radial pulse recorded on admission, pre-dose and at 2, 4, 8, 12, 24 hours post dose. Clinical examination was done at admission and discharge of each period. Clinical examination was also done at other time when the medical officer/ physician felt it necessary. AE/ well being monitoring were done on admission, pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24hours post dose in each period. Laboratory parameters of hematology and biochemistry were repeated at 24 hours post dose of the last period of the study.

## RESTRICTIONS AFTER DOSING DURING STUDY

- **Medication**
  All subjects were instructed not to take any other medications including OTC during the 2 weeks period prior to the onset of the study. The medication was advised only in cases of medical emergencies.
- **Diet**
  All subjects abstained from any xanthine containing food or beverages or alcoholic products for 48 hours prior to dosing and throughout the sampling schedule during each period.
- **Activity**
  All subjects were dosed while seated and were asked to remain seated or ambulatory for the first 2 hours following each drug administration in each period. Thereafter, subjects were allowed to engage only in normal activities while avoiding severe physical exertion.

## WASHOUT PERIOD

The administration of each product was followed by a sufficiently long period of time to ensure complete elimination of the drug(washout period) before the next administration. A wash out period of 7 days was enforced between the administrations of study drugs in each period.

## SAMPLE SCHEDULE

A total of 44 blood samples (1 × 05 ml each) (except pre-dose sample which was 10 ml) were collected into K2EDTA vacutainers under low light in pre labeled & pre chilled from each subject for pharmacokinetic analysis during the course of the study through an indwelling cannula placed in a forearm vein till 12 hours post-dose blood sample collection. At each time point collection tubes were placed in wet ice- bath immediately after collection. The blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 10.00, 12.00, 16.00, 20.00, 24.00 hours post dose in each period.

# METHOD OF MEASUREMENT

## DESCRIPTION

A developed and validated Liquid chromatography mass-spectrometry tandem mass-spectrometry (LCMS/MS) method was used for estimation of Rizatriptan in human plasma by MAXALT- MLT as an internal standard.

## DRUG ANALYSIS

### Chemicals Used

*Dilution Solution*

500 ml, of methanol and 500 ml of water were transferred into in a 1000 ml reagent bottle. It was mixed well and sonicated at ultrasonic bath. Solution was used the till next day from its date of preparation and stored at room temperature.

*5Mm Ammonium Acetate Solution*

385.40 ± 15.42 mg of ammonium acetate was transferred into a 1000 ml volumetric flask. 100 ml of water was added to dissolve completely and volume was made up to the mark with It was mixed well and sonicated at ultrasonic bath. Solution was used the till next day from its date of preparation and stored at room temperature.

*Mobile Phase*

800 ml of methanol and 200 ml of 5mM Ammonium Acetate solution was transferred into 1000 ml reagent bottle. 1 ml of formic acid was added and mixed well and sonicated at ultrasonic bath. Solution was used the till next day from its date of preparation and stored at room temperature.

*Rinsing Solution*

Methanol was used as rinsing solution and stored at room temperature.

## RESULT AND DISCUSSION

When the study was complete in FCRL during the period of Oct to March, the analysis of samples was done in the house itself by various technique which is favourable to do analysis of samples collected from the volunteer's and by the suitable methods for findings of the (sd), mean plasma concentration-time profiles of Rizatriptan, following oral administration of this compound in healthy males and females are depicted. In males, arithmetic mean AUC values were 16, 33, 72, and 127 ng $ml^{-1}$ h following doses of 2.5, 5, 10, and 15 mg, respectively, the dose-adjusted AUC geometric means were 14.3, 15.8, 17.1, and 19.8 ng $ml^{-1}$ h over the same dose range. The AUC geometric mean ratios (90% C.I.) for the 5, 10, and 15 mg treatments relative to the 2.5 mg treatment were 1.10 (0.98, 1.24), 1.19 (1.06, 1.34), and 1.38 (1.23, 1.56), respectively. The upper limit of the 90% C.I. fell outside the interval of 0.70 to 1.43 for the 15 mg dose. In men, $C_{max}$ showed generally consistent results to those reported for AUC. The $C_{max}$ geometric mean ratios (90% C.I.) for the 5, 10, and 15 mg treatments relative to the 2.5 mg treatment were 1.05 (0.88, 1.24), 1.14 (0.97, 1.35), and 1.22 (1.03, 1.45), respectively. The upper limit of the 90% C.I. fell outside the interval of 0.70 to 1.43 for the 15 mg dose. Thus, the plasma concentrations of oral Rizatriptan in males increased proportionately with doses up to 10 mg but disproportionately from 10 to 15 mg.

## DISCUSSION

The present study was performed to evaluate the pharmacokinetic parameters of the test product to the reference product of the Rizatriptan.

## CONCLUSION

The study was conducted according to the approved protocol, SOPs and ICH-GCP guidelines and applicable regulatory guidelines. A validated bioanalytical method was adopted for conduct of analysis of the plasma samples of the study, which was selective, sensitive and cost effective. Based on geometric mean ratio of log transformed data and 90% confidence interval of test and reference product for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, it is concluded that the ratio and extent of absorption of test and reference product are similar. Further it is suggested that the pharmacokinetic evaluation carried out should be performed on a larger sample size so as to statistically prove the bioequivalence of the two formulation of the Rizatriptan as per the current regulatory guidelines and GCP guidelines.

## ACKNOWLEDGMENT

The author sincerely thanks to Dr. Avijit Majumder & Mrs Akanksha Sharma for rendering his suggestions and helping them in each and every step of completing this research paper successfully.

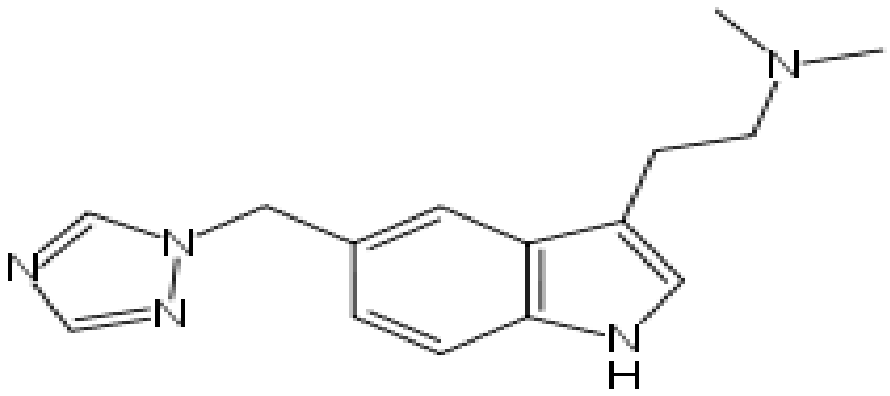
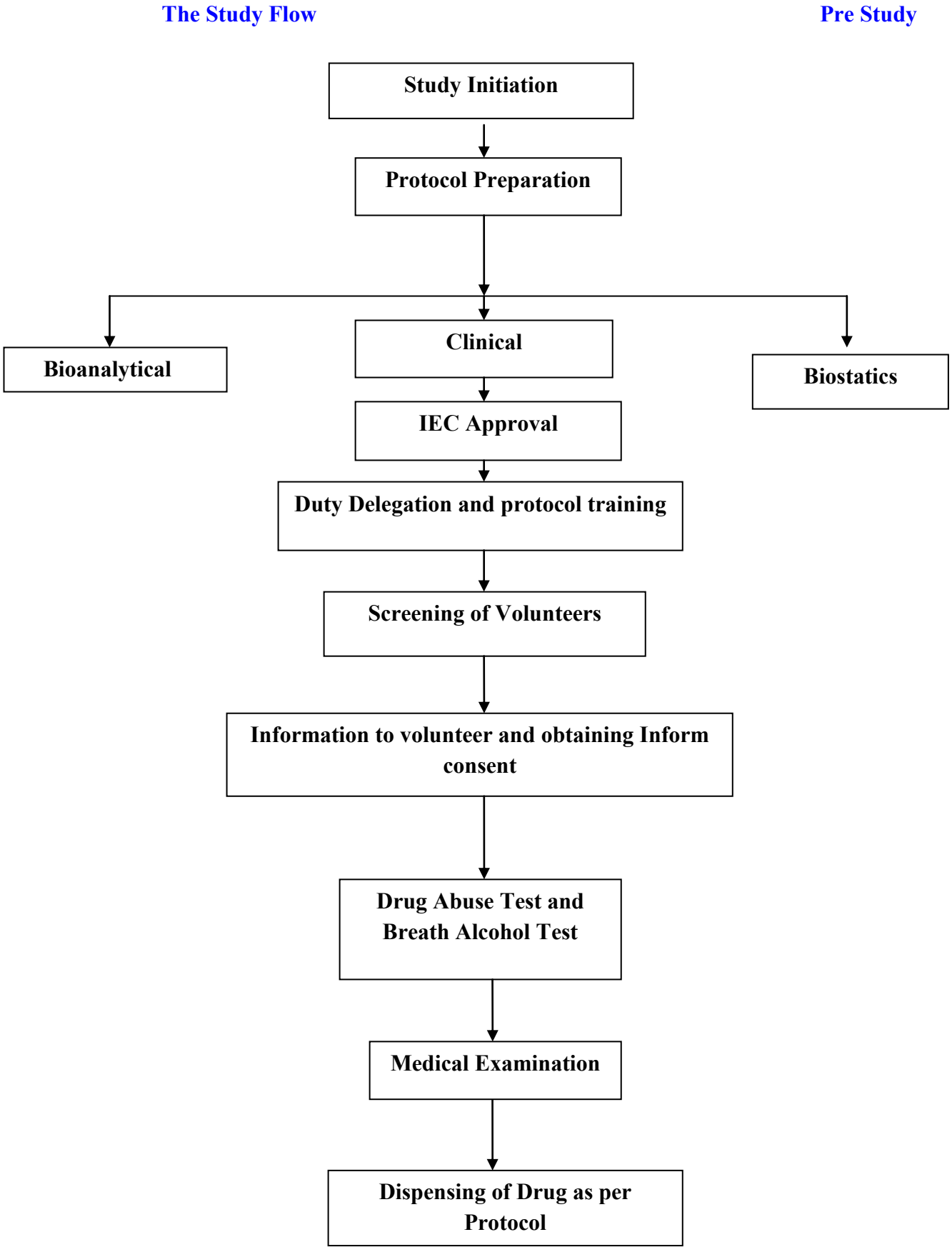


**Figure 1:** N, N-dimethyl-5-(1H-1, 2, 4-triazol-1-ylmethyl)-1H-indole-3-ethanamine

## FLOW CHART SHOWING THE STEPS OF CONDUCTION OF STUDY MATERIAL & METHODS



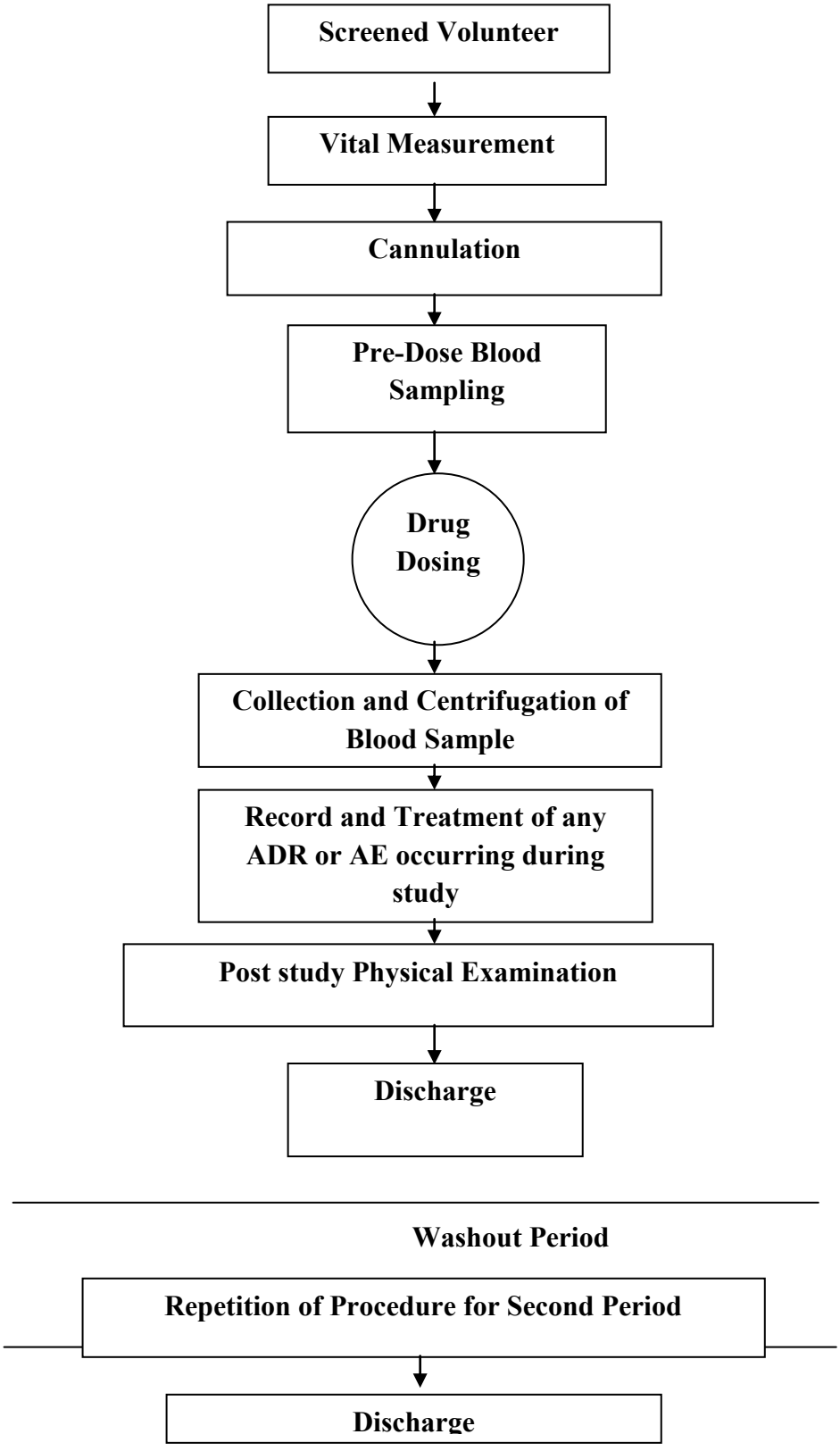



**Table 1:** Pharmacokinetic parameters

| Parameter | Rizatriptan |
|---|---|
| $T_{max}$ | 1.6 – 2.5 hrs |
| $C_{max}$ [2] | 20 ± 4.9 ng/ml |
| $T_{½}$ | 2-3 hrs |

**Table 2:** Equipments used in laboratory for analysis

| Equipment | Manufacturer | Model |
|---|---|---|
| Analytical Balance | Sartorius | CP225D |
| Automatic Pipettes | Thermoelectron | 4500090, 4500120, 4500110,4642090, 4642080, 4642070 |
| Auto Sampler | Shimadzu | SIL –HTC |
| Cold Room | Blue Star | LGZ 050 |
| Column Oven | Shimadzu | CTO -20 A |
| Degasser | Shimadzu | DGU -20 A3 |
| Digital alcohol detector | CE | CA 2000 |
| ECG | GE medical system | MAC 1200 ST |
| Height weight machine | SECA GMBH and company | SECA |
| Handy Step Dispenser | Brand | 705100 |
| Intra venous cannula | Medict | |
| Mass Spectrometer | AB SCIEX | API 4000 |
| Micro Balance | METTLER TOLEDO | XP2U |
| | Sartorius | SE2 |
| Nitrogen evaporator | Caliper | Turbo vap I.V |
| Positive Pressure | Orochem | 48PSP |
| Pump | Shimadzu | LC-20AD |
| pH meter | Thermoelectron | Orion Dual Star |
| Refrigerator | Voltas ,Samsung | ACCX21WD,RT26M |
| Reciprocating shaker | Jeotech | SK-600 |
| Refrigrated centrifuge | Heareus | Multifuge JSR |
| Syringe | Dispo –van | - |
| Stethoscope | Microtone | - |
| Sphygmometer ( BP instrument) | Diamond | Deluxe |
| Ultra Sonicator | Branson | 5510 |
| Vortex Mixer | Spinx | N/AV |
| Vacuum pump | Gast | Elix -10 gradient |
| Vaccutainer | BD | |
| X-Ray View Box | MEX India | |

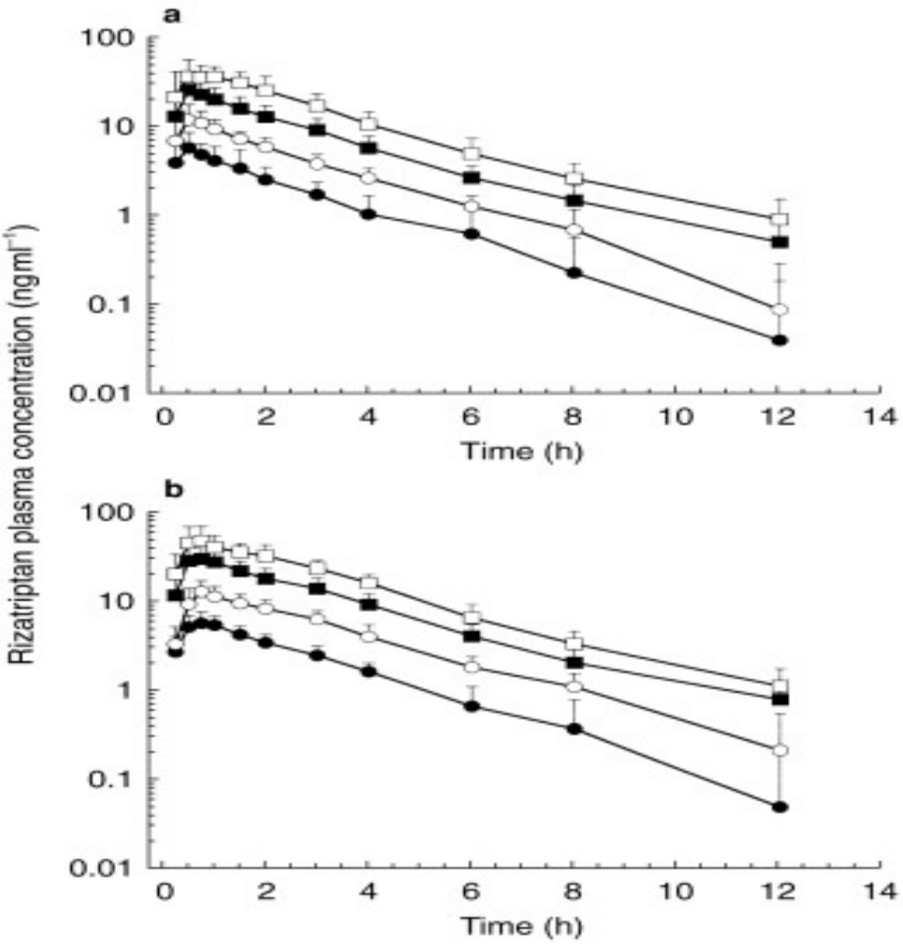



**Figure 1:** Mean Plama Concenteration v/s Time Profile

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**Cite This Article:** Hemant, Kumar; Avijit, Majumder and Akanksha, Sharma (2014), "Bioequivalence Study of Antimigraine Drug in Healthy Adult Human Subjects under Fed Conditions", ***Pharmacophore***, Vol. 5 (2), 287-300.