

## Pharmacokinetics of Bioadhesive, Gastroretentive, Controlled Release Tablets of Itraconazole: (Spherazole™ CR) in Beagle Dog Model

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### ABSTRACT SUMMARY

The pharmacokinetic profiles of Spherazole™ CR tablets and Sporanox® capsules were assessed after a single dose administered in fed beagle dogs. Spherazole™ CR tablets showed similar bioavailability, reduced  $C_{max}$  and reduced variability compared to the Sporanox® capsules.

**KEYWORDS:** itraconazole, bioavailability, pharmacokinetics, bioadhesive polymers, poly[fumaric-co-sebacic anhydride], p[FA:SA] 20:80

### INTRODUCTION

The superior bioadhesive properties of polyanhydride polymers have enabled the design of controlled release delivery systems that are gastro-retentive for extended duration<sup>1</sup>. These systems offer several distinct advantages such as (1) less prone to gastric emptying resulting in reduced intra- and inter-subject variability in plasma drug levels; (2) effective for delivery of drugs with narrow absorption windows; (3) reduced dosing and increased patient compliance; (4) reduced  $C_{max}$  and prolonged drug levels above the minimum effective concentration.

Itraconazole is a synthetic triazole anti-fungal agent with a broad spectrum of activity against *Candida* and other yeasts, dermatophytes and pathogenic fungi and is widely used for the treatment of local and systemic fungal infections. As per Biopharmaceutics Classification System, itraconazole is classified as a class II drug due to its poor water solubility ( $S < 1 \mu\text{g/mL}$ ) and low bioavailability (~50%).

The oral bioavailability of itraconazole is known to be highly dependent on food intake and, therefore, Sporanox® capsules should be taken immediately after a full meal to ensure maximum absorption. Antifungal activity of itraconazole is concentration-time dependent. Itraconazole is most effective when drug concentration is maintained above the minimum effective concentration (MEC)<sup>4</sup>. Studies in immuno-compromised patients have shown that plasma concentration below the MEC not only results in poor clinical response but may cause relapse of disease<sup>5</sup>.

Itraconazole has extremely variable and erratic oral absorption and results in marked intra- and inter-subject variability. Due to this inherent variability, it is recommended that plasma itraconazole concentration be maintained to avoid untoward side effects as well as to achieve the desired clinical response<sup>6</sup>. In addition, reports of liver impairment and cardiac toxicity have been linked to higher maximum plasma concentration<sup>7,8</sup>.

A Spherazole™ CR tablet formulation containing the bioadhesive polymer, poly[fumaric-co-sebacic anhydride] or p[FA:SA] 20:80, was designed to reside for greater than 6 hrs in the stomach. The bioadhesive tablets were less prone to gastric emptying and released itraconazole in a controlled and reproducible manner.

### EXPERIMENTAL METHODS

Cohorts of six, female beagle dogs (10-12 kg) were dosed after a standard meal either with a 100 mg Sporanox® capsule or Spherazole™ CR tablet. For plasma analysis of itraconazole, blood samples were drawn prior to dosing and at 1, 4, 8, 12, 16, 18, 24 and 48 hrs post-dosing. Plasma samples were collected and stored at -20°C until analyzed. Plasma itraconazole and hydroxyitraconazole levels were determined by liquid chromatography with MS/MS detection (LC-MS/MS). The LC-MS/MS assay was validated over the range of 10 to 500 ng/mL for both analytes. Non-compartmental calculations were used to calculate the plasma concentration versus time curves ( $AUC_{0-48}$ ). Maximum observed concentration ( $C_{max}$ ), and time at which  $C_{max}$  was observed ( $t_{max}$ ) were determined from the plasma concentration time profiles.

### RESULTS AND DISCUSSION

In a separate study, fluoroscopy was conducted on dogs dosed with Spherazole™ CR tablets 30 minutes after feeding. The tablets resided in the stomach for a minimum of 6-8 hrs and resided predominantly in the same location, in close apposition to mucosa. The prolonged gastric residence time was attributed to the bioadhesion of p[FA:SA] polymer in the composition.

Results of a pharmacokinetic study with a typical Spherazole™ CR formulation are shown in Figure 1. The  $C_{max}$  of the Spherazole™ CR formulation was approximately two-thirds relative to the  $C_{max}$  for Sporanox® capsule. The bioadhesive formulation maintained AUC similar to Sporanox® capsule. The  $t_{max}$  of the CR formulation was 8 hrs compared to 2 hrs for Sporanox® capsules. Prolonged plasma concentrations of itraconazole were observed with Spherazole™ CR compared to Sporanox®.

Based on encouraging results obtained with the Spherazole™ CR formulations, several CR formulations differing in itraconazole release rate, were tested further in dogs. The results of these four formulations are shown in Figures 2 and 3. The formulations had equivalent or superior AUC with reduced variability compared to Sporanox® capsules (Figure 2) and three of the four formulations had substantially lower  $C_{max}$  and lower variability compared to Sporanox® (Figure 3). The observed reduction in variability is probably due to the

extended gastric residence time of the bioadhesive tablets that resisted rapid gastric emptying.

### CONCLUSION

Spherazole™ CR tablets containing p[FA:SA] bioadhesive polymer were shown to be gastro-retentive for at least 6-8 hrs in the fed state in beagle dogs, an animal model characterized by rapid gastric emptying and GI transit. Bioadhesive tablets enabled extended release of itraconazole to the target absorptive sites. The dosage form resisted gastric emptying resulting in significant reduction in fluctuations in AUC and C<sub>max</sub> compared to Sporonox®. Spherazole™ CR tablets had equivalent AUC to Sporonox® capsules and maintained plasma concentrations up to 24 hrs..

### REFERENCES

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2. Sporonox® Prescribing Information.( Janssen Pharmaceutica Products LP)

Sporonox® 100 mg Capsule/ Janssen Pharmaceutica Products L.P., USA) in fed beagle dogs, n=6.

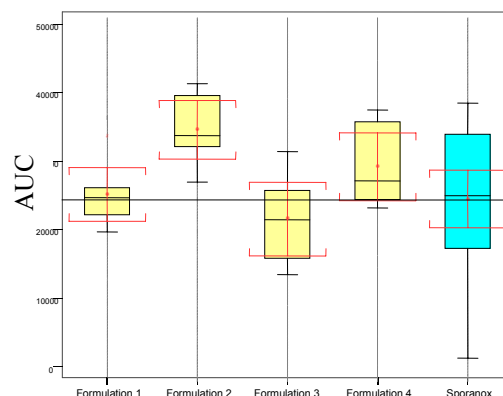


Figure 2. Box plot showing reduced variability and equivalent AUC values of four Spherazole™ CR formulations compared to Sporonox® capsules, n=6.

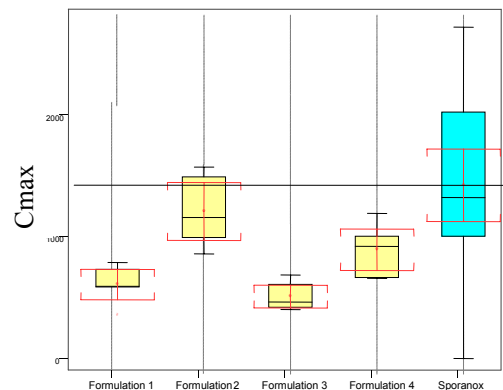


Figure 3. Box plot showing reduced variability and lower C<sub>max</sub> values of four Spherazole™ CR Formulations compared to Sporonox® capsules, n=6

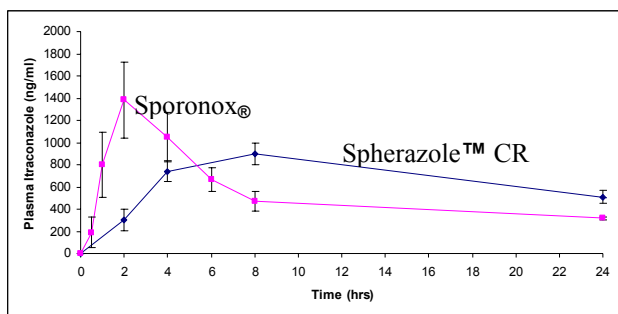


Figure 1. Mean Itraconazole plasma concentration versus time curves following a single dose of Spherazole™ CR 100 mg Tablet, Spherics Inc., USA) or a single dose of