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APPLICATION NUMBER:

22-055

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NDA#	22-055
PRODUCT	Retapamulin (Altabax)
FORMULATION	Topical ointment, 1%
SUBMISSION DATES	June 12, 2006
SUBMISSION TYPE	Original New Drug Application
SPONSOR	GlaxoSmithKline, Inc, Philadelphia, PA 19101-7929
OCPB DIVISION	Division of Clinical Pharmacology 4
MEDICAL DIVISION	Division of Anti-Infective and Ophthalmology Products
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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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1. EXECUTIVE SUMMARY

On July 6, 2006, GlaxoSmithKline submitted a second NDA (NDA 22-055) to market retapamulin ointment, 1% for the treatment of impetigo (up to 100 cm² in total area [up to 10 lesions]) due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*. The proposed dosage regimen of retapamulin ointment, 1% in pediatric and adult patients is application of a thin layer of ointment to the affected area twice daily for 5 days. The treated area may be covered with a sterile bandage or gauze dressing if desired.

In support of _____ the sponsor performed six Phase 1 clinical studies to assess the safety, tolerability, irritation potential, sensitization potential, single- and multiple-dose pharmacokinetics, metabolic profile, and drug-drug interaction potential with ketoconazole. A single Phase 2 clinical trial was performed to evaluate the pharmacokinetics, safety, and efficacy of retapamulin ointment, 1%, in patients ≥ 18 yrs of age with uncomplicated bacterial skin infections. The sponsor also performed three Phase 3 clinical trials to support the safety and efficacy of retapamulin ointment, 1% compared to oral cephalexin in _____

_____ The Phase 1 studies submitted to _____ are supportive of the clinical pharmacology of retapamulin for NDA 22-055. No additional clinical pharmacology studies were submitted with NDA 22-055.

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 4 (OCP/DCP 4) has reviewed NDA 22-055 and it is acceptable from a clinical pharmacology perspective.

1.2 PHASE IV COMMITMENTS:

No Phase IV commitments are recommended.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Below is a summary of the clinical pharmacology and biopharmaceutics findings submitted with _____ in support of NDA 22-055. Please refer to the final clinical pharmacology review for _____ dated September 25, 2006 for further details.

Pharmacokinetics in Healthy Subjects

Following single and repeat administration of retapamulin ointment, 0.5, 1, or 2% on intact skin of healthy subjects, plasma concentrations of retapamulin were generally below the lower limit of quantitation (0.5 ng/mL) following a single dose and on day 1 of repeat administration.

In general, there was higher systemic absorption in abraded skin versus intact skin when comparing day 1 exposure (single and repeat dose) on abraded skin to day 1 exposure (single and repeat dose) on intact skin. As the ointment strength (percentage of retapamulin) increased from 0.5% to 2.0% for day 1 exposure on abraded skin, the mean AUC₀₋₂₄ and C_{max} increased about 4-fold, indicating exposure increased proportional to ointment percentage. However, as the dose (ointment strength and surface area) increased from 0.5% \times 100 cm² [5 mg applied] to 1% \times 200 cm² [20 mg applied] on abraded skin, the increase in exposure was more than 4-fold indicating that surface area appears to be a more important factor for systemic exposure than the ointment strength.

For intact skin, there was an increase in exposure on day 7 compared to day 1 (repeat administration), indicating that there is some degree of accumulation following repeat daily topical applications of retapamulin ointment. Plasma concentrations of retapamulin were above the lower limit of quantitation for 147 of 187 blood samples following repeat administration and ranged from [REDACTED]. The median concentration was 2.759 ng/mL.

For abraded skin, day 7 exposure was less or similar to day 1 exposure, suggesting that healing to abraded skin by day 7 may account for the lower exposure on day 7 versus day 1. For example, plasma concentrations of retapamulin were above the lower limit of quantitation for 46 of 54 blood samples on day 1 following application of 0.5% ointment on abraded skin (100 cm²) and concentrations ranged from [REDACTED]. On day 7, plasma concentrations were above the lower limit of quantitation for 30 of 54 blood samples and ranged from [REDACTED].

Pharmacokinetics in Patients

Following application of retapamulin ointment, 1% twice daily for 5 days to adult patients (≥18 yrs of age) with uncomplicated bacterial skin infections (maximum lesion size of 100 cm² or 10 cm in length; maximum amount of drug applied per dose to a subject was 10 mg per cm²), systemic absorption was minimal and plasma concentrations of retapamulin were generally below the lower limit of quantitation. Only 9 out of 355 samples (7 out of 35 subjects) had measurable retapamulin concentrations ranging from [REDACTED]. There was no accumulation with repeat administration (twice daily for 5 days).

Absorption

The systemic absorption of topically applied retapamulin ointment, 1% is minimal in pediatric and adult patients following repeat applications to uncomplicated bacterial skin infections [REDACTED] based on the small number of quantifiable plasma concentrations.

The percentage of patients with measurable concentrations appeared to increase with increasing wound size, presumably due to the larger total dose administered and larger surface area of the wound. Unexpectedly, there was no apparent relationship between wound size and the magnitude of the observed concentration. The percentage of measurable samples also seemed to increase from non-occlusive to semi-occlusive to occlusive dressing.

Distribution

The mean plasma protein binding of retapamulin in human plasma was 93.9% and ranged from 93.2% to 94.0% over the concentration range of [REDACTED].

Metabolism

In vitro studies were performed with human liver microsomes, Supersomes, and hepatocytes to identify metabolites of retapamulin and the CYP450 isoenzymes involved in the metabolism of [¹⁴C]-retapamulin. Following incubation with microsomes, [¹⁴C]-retapamulin was extensively metabolized. The predominant routes of metabolism observed were mono-oxygenation and N-demethylation. The most prominent metabolites present in human liver microsomes were five mono-oxygenated metabolites, a N-demethylated metabolite, and a mono-oxygenation in combination with N-demethylated metabolite.

Following incubation of [¹⁴C]-retapamulin with hepatocytes, the results were similar to human liver microsomes and the routes of metabolism observed were predominantly mono-oxygenation and di-oxygenation. Other pathways observed were mono-oxygenation in combination with N-demethylation, di-oxygenation in combination with N-demethylation, N-demethylation, and possible tri-oxygenation.

Incubation of [¹⁴C]-retapamulin with CYP1A2, CYP2C9 and CYP2C19 Supersomes did not yield any detectable metabolites, indicating that these isoenzymes were not involved in the metabolism of retapamulin. Incubation of [¹⁴C]-retapamulin with CYP2C8 and CYP2D6 for 30 min resulted in the formation of a N-demethylated metabolite. Scaling of the metabolite formation by Supersomes to their relative content in the human liver microsomes suggests that the roles of CYP2C8 and CYP2D6 are minor in the overall formation of this metabolite.

CYP3A4 and CYP3A5 Supersomes rapidly metabolized [¹⁴C]-retapamulin. The incubation with CYP3A4 resulted in the formation of two mono-oxygenated metabolites of retapamulin. The other metabolites present were di-oxygenated and mono-oxygenated in combination with N-demethylated metabolites.

Excretion

A quantitative assessment of the excretion of retapamulin and metabolites in urine as a percentage of the administered dose has not been performed. A qualitative assessment of urine following repeat application of retapamulin ointment, 2% to healthy subjects with intact skin revealed the presence of parent compound and two N-demethylated metabolites, six mono-oxygenated metabolites, five di-oxygenated metabolites, and other metabolites.

An assessment of urine following repeat application of retapamulin ointment, 1% to healthy subjects with abraded skin revealed the presence of parent compound and two N-demethylated metabolites, eight mono-oxygenated metabolites, five di-oxygenated metabolites, two tri-oxygenated metabolites, one mono-oxygenated and N-demethylated metabolite, one di-oxygenated and N-demethylated metabolite, and other metabolites.

Drug-Drug Interactions

Based on *in vitro* metabolism studies, retapamulin appears to be primarily a substrate of CYP3A although it is also a substrate of CYP2C8 and CYP2D6 to a much smaller extent. In order to assess the impact of co-administration of retapamulin with a 3A4 inhibitor on retapamulin plasma concentrations, the sponsor conducted an *in vivo* drug-drug interaction study to evaluate the pharmacokinetics of retapamulin following a single application of retapamulin with and without ketoconazole in 26 healthy adult subjects. Subjects received 0.5 g of 1% w/w retapamulin ointment formulation (i.e., 5 mg retapamulin) on 50 cm² abraded skin with and without ketoconazole. Each application of retapamulin ointment was occluded for approximately 24 hrs, then completely removed and the skin area washed. Ketoconazole 200 mg was administered twice daily for four days with 240 mL of water. On the morning of day 4, ketoconazole was administered immediately before retapamulin was applied. There was a 7-14 day washout period between sessions.

The mean AUC₀₋₂₄ and C_{max} of retapamulin increased 80% and 77%, respectively when administered with ketoconazole 200 mg compared to administration alone. However, none of the individual retapamulin AUC₀₋₂₄ or C_{max} values exceeded the highest values observed in a previous pharmacokinetic study in healthy volunteers (Study SB-275833/026). Based on the minimal absorption and minimal quantifiable plasma concentration observed in patients with uncomplicated bacterial skin infections (Study SB-275833/029), the magnitude of these increases are unlikely to result in an increased incidence of adverse events. No dosage adjustment of retapamulin ointment, 1% is recommended when co-administered with ketoconazole or other CYP3A4 inhibitors.

Retapamulin is a poor inhibitor ($IC_{50} \geq 99 \mu\text{M}$) of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6. It is not anticipated that retapamulin will cause clinically relevant drug-drug interactions with drugs metabolized by these isoenzymes. Retapamulin inhibited CYP3A4 isoenzyme activity (IC_{50} ranged from $1.1 \mu\text{M}$ with midazolam to $6.2 \mu\text{M}$ with nifedipine). The I/K_i ratio following topical application of retapamulin ointment, 1% (assuming a mean C_{max} of approximately 2 ng/mL or $0.004 \mu\text{M}$) ranges from 0.001 to 0.004. Thus, the I/K_i ratios are less than 0.1 for all cytochrome P450 isoenzymes, including CYP3A4 and no clinically relevant drug-drug interactions of retapamulin on these substrates are anticipated when retapamulin is co-administered with other drugs metabolized by the cytochrome P450 system.

Retapamulin is an *in vitro* substrate of P-glycoprotein mediated transport and an *in vitro* inhibitor of digoxin transport via human P-glycoprotein with a calculated IC_{50} value of $28.2 \mu\text{M}$ ($14,600 \text{ ng/mL}$). Retapamulin was also found to have moderate passive membrane permeability across cells. It is unlikely that retapamulin will inhibit P-glycoprotein mediated transport of co-administered drugs.

Cardiac Repolarization

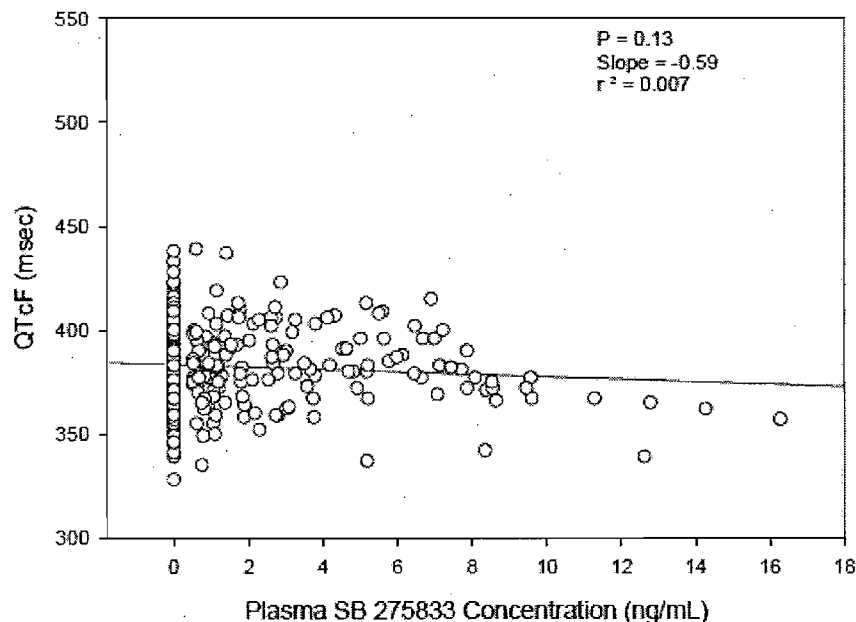
The potential of retapamulin to impact cardiac repolarization was evaluated using an *in vitro* hERG current. Retapamulin inhibited *in vitro* hERG current by (mean \pm SEM) $10.7 \pm 1.8\%$ at $1 \mu\text{M}$, $59.7 \pm 2.7\%$ at $10 \mu\text{M}$, and $96.2 \pm 0.7\%$ at $100 \mu\text{M}$. The estimated IC_{50} for the inhibitory effect of retapamulin on hERG current is $6.8 \mu\text{M}$ (equivalent to $3.52 \mu\text{g/mL}$). Based on C_{max} values from healthy subjects (Study SB-275833/026) and adult and pediatric patients (Studies SB-275833/029, SB-275833/030A, and SB-275833/030B), the *in vitro* hERG current IC_{50} is approximately 350-times the anticipated C_{max} values associated with the intended clinical use.

Since a thorough QT study was not conducted, the sponsor performed a post-hoc analysis of manually read 12-lead ECGs from Study SB-275833/026 to assess the impact of retapamulin on cardiac repolarization in healthy subjects. In this study, the sponsor evaluated the impact of single- and multiple-dose administration of three strengths of retapamulin ointment (0.5, 1, and 2% and placebo) on intact and abraded skin with varying application surface areas (400 to 1600 cm^2 on intact skin and 100 to 200 cm^2 on abraded skin). Three ECGs were obtained at baseline and up to five ECGs were obtained following administration of retapamulin ointment.

The relationship between QTcF interval and retapamulin plasma concentration from all cohorts on day 1 and day 7 is shown in Figure 1. There was no increase in the QTcF interval with increasing plasma concentrations of retapamulin from subjects with intact or abraded skin on day 1 and day 7.

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Figure 1. QTcF interval vs. retapamulin plasma concentration



No exposure-response relationship was observed with intact skin or abraded skin following a single application of retapamulin ointment, 0.5%, 1%, 2% or placebo. Similar to the results following a single application, no exposure-response relationship was observed with intact skin on day 7 with repeat applications of retapamulin ointment although an increase in the QTcF value was observed following repeat applications of retapamulin ointment, 2% on abraded skin. However, the mean plasma concentration of retapamulin following repeat applications of retapamulin ointment, 2% on abraded skin was less than repeat applications of retapamulin ointment, 1% on abraded skin due to a smaller surface area of the application site (100 cm² for 2% ointment vs. 200 cm² for 1% ointment).

Although there was a trend for increasing mean maximum change from baseline QTcF with increasing concentration of retapamulin on intact skin, the results are not supported by the lack of an exposure-response relationship following repeat application on intact skin. In addition, the increase in the mean QTcF following administration of retapamulin 2% ointment on intact skin was not supported by the maximum change from baseline QTcF on day 7 following repeat applications of retapamulin on abraded skin. Thus, no clinically meaningful relationship was observed between QTcF duration or maximum change and retapamulin dose (ointment strength), C_{max} or plasma concentration.

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