Clinical Review of an Amendment to NDA 22-055

Date of Submission: March 31, 2009

Date Assigned to Reviewer: March 31, 2009

Date Review Initiated: April 1, 2009

Drug: Altabax (retapamulin) Ointment, 1%

Applicant: GlaxoSmithKline (GSK)
P. O. Box 7929
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Indications: Altabax Ointment is indicated for impetigo due to S*taphylococcus aureus* (methicillin – susceptible isolates only) or *Streptococcus pyogenes*.

Reason for Amendment: Submission of the final report for Study TOC 106489, a required postmarketing study in the pediatric population.

Background: This NDA was approved on April 12, 2007 for the treatment of impetigo. The approval letter stated that the pediatric study requirement for the drug was waived for children aged 0 to 2 months and deferred for children aged 2 to 9 months. The drug is approved for use in children 9 months of age and older. A study in children 2-9 months was therefore required as a postmarketing study commitment.

After some negotiation, the final protocol for the required study, designated as Study no. TOC 106489, was submitted on June 22, 2007 and reviewed by DAIOP on August 3, 2007. The Applicant submitted amendments to the study protocol on December 16, 2008 which were described in the Clinical Review of January 24, 2009. The final report for this study has now been submitted and is the subject of this review.

(b) (4)

Review:

1. Protocol

The protocol for Study no.TOC 106489 has been fully described in earlier Clinical Reviews and will not be detailed here. Briefly, the study was designed to estimate the systemic absorption of Altabax in cohorts of children aged >=2 to <= 6 months, >6 to <=12 months, and >12 to <=24 months of age who had secondarily infected lesions

(SITL), secondarily infected dermatoses (SID), or impetigo. Each defined age group was intended to contain 20 evaluable patients, for a total of 60 patients. They were treated with Altabax BID for 5 days. Patients were not permitted to enter the study if more than 2% of their total body surface area was involved with disease. The patients were also required to have a SIRS (sign and symptom) score of at least 8 for disease symptomatology (pus/exudate, crusting, erythema, etc). Each subject had a blood draw made on day 3-4 of therapy for PK analysis and 10 subjects in each age cohort had blood samples taken on the same day for clinical laboratory testing. Drug efficacy was also evaluated.

The August 3, 2007 review had the following comment concerning the pediatric study protocol:

> Reviewer's Comment: This protocol adequately deals with all deficiencies/comments noted in previous reviews with one exception: the reviewer is concerned that SID patients will be the easiest to enroll (particularly in the youngest age group), thereby minimizing data gathered from the other disease entities to be studied. Therefore, GSK was asked to specify in the protocol that no more than 50% of each of the 3 specified age groups be comprised of SID patients (total 30 of 60 patients). No mention of this request is made in the protocol.

The results of this study will be presented in the following sections; demographics and disposition of subjects; PK results; adverse events; clinical laboratory results; and clinical and bacteriological results.

2. Results

a. Demographics and disposition of subjects

i. Demographics

The following table presents the demographic data for the clinical ITT population.

Table 1 Demographic Characteristics (ITTC Population)

Parameter	Retapamulin Ointment, 1% N= 86
Age (months)	
Mean (SD)	10.6 (6.89)
Median	10.0
Minimum, maximum	2, 23
Sex	
Female	n (%) 32 (37.2)
Male	n (%) 54 (62.8)
Ethnicity	
Hispanic/Latino	n (%) 29 (33.7)
Non-Hispanic/Latino	n (%) 57 (66.3)
Race[1]	
African American/African heritage	n (%) 46 (53.5)
White	n (%) 36 (41.9)
Other[2]	n (%) 3 (3.5)

ITTC=Intent-to-Treat Clinical; SD =standard deviation
1. One subject did not have their race recorded in the eCRF.
2. Includes American Indian or Alaska native, Central/South Asian heritage, and East Asian heritage

The following table presents the clinical diagnoses of the patients, stratified by age group.

Table 2 Clinical Diagnosis of Skin Infection, by Age Group (ITTC Population)

	Retapamulin Ointment, 1%			
Age Group	Impetigo	SID	SITL	All Infections
	N= 47	N= 30	N=9	N= 86
>=2 months to<=6 months	n (%) 11 (23.4)	n (%) 17 (56.7)	n (%) 1(11.1)	n (%) 29 (33.7)
>6 months to <=12 months	n (%) 18 (38.3)	n (%) 9 (30.0)	n (%) 2 (22.2)	n (%) 29 (33.7)
>12 months to <=24 months	n (%) 18 (38.3)	n (%) 4 (13.3)	n (%) 6 (66.7)	n (%) 28 (32.6)

ITTC =Intent-to-Treat Clinical; SITL =secondarily-infected traumatic lesions; SID =secondarily-infected dermatoses

Reviewer's Comment: This reviewer was concerned about an imbalance in entering diagnoses in the youngest patients (see above). While a majority of the youngest patients entering the study did have SID, there is a sufficient number of impetigo patients in this group to balance the analysis. There are few SITL patients in the study, which is probably due to the relative lack of mobility of these very young children.

The following table presents the number of patients in each disease category who had pathogens isolated at baseline.

Table 3 Number (%) of Subjects by Number of Pathogens Isolated at Baseline, by Clinical Diagnosis of Skin Infection (ITTC Population)

	Number (%) of Subjects			
Number of Baseline Pathogens	Impetigo N= 47	SID N= 30	SITL N=9	Total N=86
0	10 (21.3)	12 (40.0)	3 (33.3)	25 (29.1)
1	20 (42.6)	10 (33.3)	2 (22.2)	32 (37.2)
2	16 (34.0)	8 (26.7)	4 (44.4)	28 (32.6)
>=3	1 (2.1)	0	0	1 (1.2)
Number of subjects with at least 1 baseline pathogen	37 (78.7)	18 (60.0)	6 (66.7)	61 (70.9)

ITTC =Intent-to-Treat Clinical; SID = Secondarily-infected dermatoses; SITL = Secondarily-infected traumatic lesions

The following table lists the pathogens isolated at baseline from all subjects.

Table 4 Number (%) of Pathogens Isolated at Baseline (ITTB Population)

	Number (%) of Isolates
Baseline Pathogens[1]	Retapamulin Ointment, 1%
All Pathogens	93
S. aureus	44 (47.3)
MRSA[2]	3 (3.2)
MSSA[2]	41 (44.1)
mupSSA[3]	44 (47.3)
fusRSA[4]	2 (2.2)
fusSSA [4]	42 (45.2)
S.pyogenes	9 (9.7)
Other Gram (+)pathogens[5]	11 (11.8)
Gram (-) pathogens	29 (31.2)

1. Subjects may be represented in this table more than once as they may have had more than one pathogen at baseline.
2. MRSA/MSSA are methicillin-resistant/susceptible *S. aureus,* as defined by susceptibility to cefoxitin.
3. Mupirocin breakpoints defined as susceptible <=4 microg/mL, resistant >=8/microg/mL
4. Fusidic acid breakpoints defined as susceptible <=1 microg/mL, intermediate =2 microg/mL, resistant >=4 microg/mL
5. All Other Gram (+) pathogens were *Enterococcus faecalis.*
ITTB = Intent-to Treat Bacteriological; mupSSA =Mupirocin-susceptible *S. aureus;* fusSSA =Fusidic acid-susceptible *S. aureus;* fusRSA =Fusidic acid-resistant *S. aureus.*

ii. Disposition of subjects

The following tables present the disposition of patients by age and disease category.

Table 5 Disposition of Subjects, by Age Category, N (%)

	Retapamulin Ointment, 1%			
Population	>=2 months to <=6 months to N= 30	> 6 months to <=12 months N=29	>12 months to <= 24 months N=28	All Age Categories N= 87
Completed study	24 (80.0)	27 (93.1)	27 (96.4)	78 (89.7)
Analysis Populations				
ITTC	29 (96.7)	29 (100.0)	28 (100.0)	86 (98.9)
Subjects who provided blood sample for safety	11 (36.7)	12 (41.4)	14 (50.0)	37 (42.5)
ITTB	21 (70.0)	20 (69.0)	20 (71.4)	61 (70.1)
PK	24 (80.0)	28 (96.6)	27 (96.4)	79 (90.8)

ITTC =Intent-to-Treat Clinical; ITTB =Intent-to-Treat Bacteriological; PK =Pharmacokinetic

Table 6 Disposition of Subjects, by Infection Type at Baseline, N (%)

	Retapamulin Ointment, 1%			
Population	Impetigo N= 47	SID N=31	SITL N=9	All Infections N=87
Completed study	44 (93.6)	25 (80.6)	9(100.0)	78 (89.7)
Analysis Populations				
ITTC	47 (100.0)	30 (96.8)	9 (100.0)	86 (98.9)
Subjects who provided blood sample for safety	14 (29.8)	18 (58.1)	5 (55.6)	37 (42.5)
ITTB	37 (78.7)	18 (58.1)	6 (66.7)	61 (70.1)
PK	45 (95.7)	25 (80.6)	9 (100.0)	79 (90.8)

ITTC = Intent-to-Treat Clinical; ITTB = Intent-to-Treat Bacteriological; SITL = secondarily-infected traumatic lesions; SID = secondarily-infected dermatoses; PK = Pharmacokinetic

Reviewer's Comment: It is understandable that the protocol required relatively few patients in the youngest age cohorts to provide blood samples for clinical lab testing. However, this relatively small number of samples makes interpretation of results in terms of the general pediatric patient population difficult.

The following table presents the number of subjects evaluated at each visit.

Table 7 Number of Subjects Evaluated at Each Visit (ITTC Population.)

	Retapamulin Ointment, 1%
Study Visit/Phase	n (%)
Visit 1/Baseline	86
Visit 2/On Therapy	83 (96.5)
Visit 3/End of Therapy	81 (94.2)
Visit 4/Follow-up	78 (90.7)

The following table presents the reasons for withdrawal from the study.

Table 8 Reasons for Withdrawal from Treatment/Study (ITTC Population)

	Retapamulin Ointment, 1% N= 86 n (%)
Completion Status	
Completed	78 (90.7)
Withdrawn	8 (9.3)
Primary Reason for Withdrawal	
Adverse Event	3 (3.5)
Lost to follow-up	2 (2.3)
Protocol violation	1 (1.2)
Subject elected to withdraw	2 (2.3)
Other	0

ITTC = Intent-to-Treat Clinical

Reviewer's Comment: This study is of sufficient size to provide meaningful data on the PK and safety characteristics of very young children. The patients in the 12 to 24 month age category provide useful information, but are not the primary focus of this review.

b. PK results

Of 79 PK samples taken during this study, 36 (46%) displayed measurable (>= 0.5 ng/mL) amounts of retapamulin. The following table presents the number of measurable samples by cohort.

Table 9 Percentage of Measurable Samples, by Population

Age Bracket	>=2 months to <=6 months	> 6 months to <=12 months	>12 months to <= 24 months	All Age Categories
Total Number of Samples	24	28	27	79
Number of Measurable Samples (Range, ng/mL)	17 (0.56-177.3)	10 (0.52-3.27)	9 (0.61-95.13)	36 (0.52-177.3)
Number of Non-measurable Samples	7	18	18	43
% of Measurable Samples	71	36	33	46

Note: One PK sample was taken from each subject evaluated for PK.

Reviewer's Comment: The percentage of measurable samples in this study is much higher than the 7% figure seen in the pediatric population (136 patients aged 9 months-17 years) studied (b) (4) **It is especially noteworthy that 17/24 patients (71%) aged 2-6 months**

had measurable amounts of retapamulin in the bloodstream after 3-4 days of BID treatment. In the older age cohorts, about one-third of the patients displayed measurable amounts of the drug.

The following table presents the number of measurable samples by concentration range. The figure >18.5 ng/mL in the table was chosen because that is the highest concentration seen in any patient in the [redacted] (b) (4) data.

Table 10 Percentage of Measurable Samples as Total Number of Measurable Samples, by Concentration Range

Measurable Plasma Concentration Range (ng/mL)	>= 0.5 to <= 1.0	>1.0 to <= 2.0	>2.0 to <= 2.5	>2.5 to <= 5.0	>5.0 to <= 18.5	>18.5	Total (0.52 to 177.3)
Total Number (%) of Measurable Samples at Each Concentration .Range	9 (25)	7 (19)	6 (17)	5 (14)	4 (11)	5 (14)	36 (100)

Note: A total of 36 of 79 PK samples were measurable.

Reviewer's Comment: In this study, 14% of pediatric patients displayed blood levels higher than has been seen in previous PK testing of patients 9 months of age and older. As will be discussed later, 4 of these 5 patients were in the 2-6 month age cohort.

A number of factors (wound size, dressing type, SIRS score, type of infection) were examined to see which might be most critical in enhancing systemic exposure. The only factor which displayed a significant trend was type of infection, as represented in the following table.

Table 11 Percentage of Measurable Samples by Type of Infection

Diagnosis	Impetigo	SID	SITL	Total
Total Number of Samples	45	25	9	79
Number of Measurable Samples (Range, ng/mL)	17 (0.52-177.3)	16 (0.56-95.13)	3 (1.82- 26.9)	36 (0.52-177.3)
Number of Non-measurable Samples	28	9	6	43
% of Measurable Samples	38	64	33	46

Reviewer's Comment: In terms of percentage, more patients with SID had measurable retapamulin levels than did the impetigo or SITL patients. It is also noted, however, that there were only 9 SITL patients in the study, so interpretation for that disease classification is difficult. Patients treated for the [redacted] (b) (4) impetigo

indication may be at somewhat less risk of measurable absorption than SID patients, but it must be noted that the two highest concentrations of retapamulin seen in the study (177.3 and 174.3 ng/mL, or about 10 times the highest blood level previously observed) were in impetigo patients.

The following table presents the percentage of measurable samples by gender and race.

Table 12 Percentage of Measurable Samples by Gender and Race
(PK Population)

Subgroup	Subjects with Measurable Plasma Concentration of Retapamulin n/N[1] (%)
Gender	
Female	14/29 (48.3)
Male	22/50 (44.0)
Race	
African American/African heritage	22/43 {51.2)
White/Caucasian/European	12/32 (37.5)
American Indian/Alaskan native	1/1 (100)
Asian - East Asian heritage	1/1 (100)
Asian- Central/South Asian heritage	0/1 (0)
Unknown	0/1 (0)

1. N=Number of subjects belonging to the specific subgroup and population; n=number of subjects belonging to the specific subgroup and population and had measurable plasma concentrations of retapamulin

Note: A total of 79 subjects provided PK samples (one sample per subject).
PK =pharmacokinetic

The following table presents the number of measurable samples and concentration ranges found by age cohort and disease entity.

Table 13 Number of Measurable Samples and Range of Concentrations, by Age Group and Type of Lesion (PK Population)

Skin Infection and Age Group	n	Range ng/ml
Impetigo	17	0.520, 177.29
>=2 months to <=6 months	8	0.840, 177.29
>6 months to <=12 months	4	0.520, 1.29
>12months to <=24 months	5	0.611, 13.03
SID	16	0.562, 95.13
>=2 months to <=6 months	8	0.562, 80.32
>6 months to <=12 months	5	0.793 3.27
>12 months to <=24 months	3	1.16, 95.13
SITL	3	1.82, 26.92
>=2 months to <=6 months	1	26.92, 26.92
>6 months to <=12 months	1	1.82, 1.82
>12 months to <=24 months	1	2.54, 2.54

PK = Pharmacokinetic; SID = Secondarily-infected dermatoses; SITL = secondarily-infected traumatic lesions
Note: A total of 36 samples were measurable

The following table summarizes the status of the 5 children who displayed retapamulin levels greater than18.5 ng/mL during the study.

Table 14 Subjects with High Retapamulin Plasma Concentrations

Subject No.	Gender	Race	Cp (ng/mL)	Age (month)	Age Group	Infection Type	Wound Size (cm^2)	Dressing Type	SIRS Score
284	M	African American/ African Heritage	177.3	4	>=2 to <=6 mo	Impetigo	1.44	None	10
109	F	Caucasian/ European Heritage	174.3	4	>=2 to <=6 mo	Impetigo	0.25	Semi-occlusive	19
169	M	African American/ African Heritage	95.1	21	>12 to <=24 mo	SID	1	None	9
314	M	African American/ African Heritage	80.3	2	>=2 to <=6 mo	SID	6	None	18
287	M	African American/ African			>=2 to				

Heritage	26.9	3	<=6 mo	SITL	25	None	20

Reviewer's Comment: **These results must be interpreted with caution, because the database is relatively small. The following comments are offered:**

1. Retapamulin absorption in infants is possible at much higher levels than were found in older (9 months to adult) populations.

2. Children 2-6 months of age are more vulnerable to absorption of retapamulin at any level and to relatively high levels of absorption than are older pediatric patients and adults.

3. This absorption phenomenon does not appear to be directly related to wound size or SIRS score on study entrance, but may be related to disease entity, as SID patients were more likely to exhibit measurable absorption than SITL or impetigo patients.

4. Because drug levels were analyzed from samples taken on day 3-4 of a 5-day therapy regimen, it is possible that higher retapamulin levels than are reported here were seen at end of therapy.

5. Patient no. 109, who had a plasma who had a retapamulin plasma concentration of 174.3 ng/mL, also had an elevated ALT (66 IU/L) at the end of therapy visit. No other adverse reactions were reported in the cohort with high drug plasma concentrations.

6. The original pharmacology/toxicology review for retapamulin was performed by Dr. Rafie-Kolpin (b) (4) **Results were that monkeys, rats and rabbits tolerated the drug well in amounts up to 3 mg/kg in a single dose or 0.1% when given daily.**

7. Children of African-American/African heritage may be more likely to absorb retapamulin at relatively high levels. However, given the relatively small number of subjects and lack of physiologic basis for such a phenomenon, this is unlikely.

In general, it is difficult to assess whether the levels seen in these children predict systemic toxicity. (b) (4)

iii. Adverse events

The following table lists the adverse events seen in the study by age cohort (note that some patients experienced more than one AE).

Table 15 Adverse Events, by Age Group (ITTC Population)

Retapamulin Ointment, 1%

Preferred Term	>=2 months to <=6 months N=29 n (%)	> 6 months to <=12 months N=29 n (%)	>12 months to <= 24 months N=28 n (%)	All Age Categories N=86 n (%)
Any adverse event	4 (13.8)	4 (13.8)	3 (10.1)	11 (12.8)
Diarrhea	1 (3.5)	0	1 (3.6)	2 (2.3)
Atopic dermatitis	1 (3.5)	0	1 (3.6)	2 (2.3)
Influenza	0	1 (3.5)	1 (3.6)	2 (2.3)
Abdominal pain	0	1 (3.5)	0	1 (1.2)
Vomiting	0	1 (3.5)	0	1 (1.2)
Dermatitis	0	1 (3.5)	0	1 (1.2)
Impetigo	0	0	1 (3.6)	1 (1.2)
Skin fissures	1 (3.5)	0	0	1 (1.2)
Hypersensitivity	1 (3.5)	0	0	1 (1.2)
Cough	1 (3.5)	0	0	1 (1.2)
Pharyngitis	0	1 (3.5)	0	1 (1.2)
Hypochromatic anemia	0	1(3.)	0	1 (1.2)

ITTC = Intent-to-Treat Clinical

Three subjects withdrew from the study due to adverse events. The first was a 2 month old female being treated for atopic dermatitis who developed hypersensitivity (rash) on her face on day 2 of the study. She was withdrawn from the study and the event resolved after 2 days. The investigator considered this reaction to be due to study treatment.

The second event concerned a 16 month old male treated for impetigo of the trunk who developed disseminated lesions on the elbow and knee on day 2 of treatment. He was withdrawn from the study on day 3 and treated with Cefdinir. The impetigo resolved after 12 days. The investigator considered this event to be related to treatment, though it might be more accurately defined as lack of effectiveness. The patient had positive baseline cultures for *Acinetobacter, E. faecalis* and *Leclercia adecarboxylata* in addition to *S. aureus.*

The last case concerns a 3 month old male who received the full 5 day course of retapamulin. He developed a mild cough on day 4 of therapy and a severe cough one day after therapy ended. On the same evening, he died suddenly. The investigator stated that the cause of death is unknown, with possibilities being SIDS or pneumonia. No autopsy was performed, and the parents were unwilling to cooperate with follow-up. This child had a plasma concentration of 2.89 ng/mL on day 3 or 4 of therapy. It is unlikely that retapamulin contributed this death.

There was one other event described because concomitant therapy was used. A 3 month old female who was being treated with retapamulin for atopic dermatitis on the right side

of her scalp and neck was treated at the same time with mupirocin for a fissure on the back portion of her left ear.

iv. Clinical laboratory results

As noted above, there were relatively few blood samples taken for analysis of clinical labs (37 of 87 subjects were sampled). Therefore, it is difficult to determine patterns in this information. Values which were outside normal parameters were in general scattered among the sampled subjects. The following table presents subjects with post-baseline lab values which were of potential clinical concern as judged by guidelines provided by FDA.

Table 16 Subjects with Post-Baseline Clinical Chemistry Laboratory Test Values of Potential Clinical Concern (FDA Criteria)

Analyte	Subject Number	Visit	Value
AST (lU/L)	041702/35	Baseline	75
		On Therapy	88
	045261/74	Baseline	41
		On Therapy	44
ALT (lU/L)	032374/109	Baseline	40
		On Therapy	66

Patient 109 had a retapamulin plasma concentration of 174.3 ng/mL and was discussed above.

The following table presents the subjects with post-baseline hematology values which were of potential clinical concern using guidelines provided by FDA.

Table 17 Subjects with Post-Baseline Hematology Laboratory Test Values of Potential Clinical Concern (FDA Criteria)

Analyte	Subject Number	Visit	Value
Eosinophils (GI/L)	032374/110	Baseline	0.35
		On Therapy	0.89
	032374/111	Baseline	1.63
		On Therapy	1.91
Neutrophils (GI/L)	041702/35	Baseline	1.01
		On Therapy	0.79
	033057/173	Baseline	2.22
		On Therapy	0.80

Patient no. 110 had AE's of atopic dermatitis and diarrhea in addition to the elevated eosinophil value noted above. This subject also had hemoglobin and hematocrit values below the normal range at study entrance and while on therapy.

v. Clinical and bacteriological results

This was an open study, with results from a number of investigators. Some trends can be observed in the results, however. The following table presents the clinical response at the follow-up visit by age cohort. Please note that a clinical response of "success" includes patients who were completely cured of all disease signs and symptoms as well as those who displayed some degree of clinical improvement and did not require further therapy after the last day of retapamulin treatment.

Table 18 Clinical Response at Follow-up, by Age Group and Analysis Population

		Retapamulin Ointment, 1%			
		ITTC N=86		ITTB N=61	
Age Group	Clinical Response	n (%)	95%CI	n (%)	95%CI
>=2 months to <=6 months	Success	22 (75.9)	(56.5, 89.7)	18 (85.7)	(63.7, 97.0)
	Failure	7 (24.1)		3 (14.3)	
>6 months to <=12 months	Success	26 (89.7)	(72.7, 97.8)	17 (85.0)	(62.1, 96.8)
	Failure	3 (10.3)		3 (15.0)	
>12 months to <=24 months	Success	27 (96.4)	(81.7, 99.9)	19 (95.0)	(75.1, 99.9)
	Failure	1 (3.6)		1 (5.0)	

CI= confidence interval; ITTB = Intent-to-Treat Bacteriological; ITTC = Intent-to-Treat Clinical

The following table presents clinical success rates by age and infection classification.

Table 19 Clinical Success Rate at Follow-up, by Age Group and Type of Infection (ITTC Population)

	Retapamulin Ointment, 1%	
Clinical Diagnosis of Skin Infection and Age Category	Clinical Success/N	Clinical Success Rate (%)
Impetigo		
>=2 months to <=6 months	10/11	90.9
>6 months to <=12 months	17/18	94.4
>12 months to <=24 months	17/18	94.4
SID		
>=2 months to <=6 months	11/17	64.7
>6 months to <=12 months	7/9	77.8
>12 months to <=24 months	4/4	100
SITL		
>=2 months to <=6 months	1/1	100
>6 months to <=12 months	2/2	100
>12 months to <=24 months	6/6	100

ITTC =Intent-to-Treat Clinical; SID =Secondarily-infected dermatoses; SITL =secondarily-infected traumatic lesions

Reviewer's Comment: It is noted that the relatively poor performance of retapamulin in the 2-6 month age cohort is principally due to failures in SID patients. (b) (4)

The following table presents the overall bacteriological success rates by age group at follow-up.

Table 20 Bacteriological Response at Follow-up by Age Group

		Retapamulin Ointment, 1%	
Age Group	N	Bacteriological Successes	Success Rate
All	61	51	83.61%
>=2 to <=6 months	21	15	71.43%
>6 to <=12 months	20	17	85.00%
>12 to <=24 months	20	19	95.00%

The following table presents the bacteriological success rates by age group and disease entity at follow-up.

Table 21 Bacteriological Response at Follow-up by Age Group and Infection type

Clinical Diagnosis of Skin Infection and Age Group	Retapamulin Ontment, 1% Successes/N#	Success rate
Impetigo		
>=2 to <=6 months	7/8	87.50%
>6 to <=12 months	14/15	93.33%
>12 to <=24 months	13/14	92.86%
Secondarily infected dermatoses (SID)		
>=2 to <=6 months	7/12	58.33%
>6 to <=12 months	2/4	50.00%
>12 to <=24 months	2/2	100.00%
Secondarily infected traumatic lesion (SITL)		
>=2 to <=6 months	1/1	100.00%
>6 to <=12 months	1/1	100.00%
>12 to <=24 months	4/4	100.00%

Reviewer's Comment: As in the clinical effectiveness data, the relative lack of bacteriological success in the 2-6 month age cohort is driven by SID patients.

The following table presents the bacteriological success rates for various pathogens at follow-up.

Table 22 Bacteriological Success Rate at Follow-up, by Baseline Pathogen (ITTB Population)

Baseline Pathogen	Retapamulin Ointment, 1% n/N[1]	Success Rate (%)
All Pathogens	76/93	81.7
Staphylococcus aureus	40/44	90.9
MRSA[2]	3/3	100
MSSA[2]	37/41	90.2
mupSSA[3]	0/44	90.9
fusRSA[4]	2/2	100
fusSSA[4]	38/42	90.5
Streptococcus pyogenes	9/9	100
Other Gram (+) pathogens[5]	6/11	54.6
Gram (-) pathogens	21/29	72.4

1. n/N = number of clinical successes/number of pathogens isolated at baseline. Subjects may be represented in this table more than once as they may have had more than one pathogen isolated at Baseline.
2. MRSA/MSSA are methicillin resistant/susceptible *S. aureus*, as defined by susceptibility to cefoxitin
3. Mupirocin breakpoints defined as susceptible ≤4μg/mL, resistant ≥8μg/mL
4. Fusidic acid breakpoints defined as susceptible ≤1μg/mL, intermediate =2μg/mL, resistant ≥4μg/mL.

5. All Other Gram-positive pathogens were *Enterococcus faecalis*.
NA = not applicable; mupSSA = mupirocin-susceptible *S. aureus*; fusSSA = fusidic acid-susceptible *S. aureus*; fusRSA =fusidic acid-resistant *S. aureus*

Conclusions and Recommendations: This study establishes that retapamulin is absorbed much more frequently in the youngest children tested than previously observed in the more mature pediatric population. Further, absorption reaches higher levels in these children than has been observed in older patients. The significance of this information is unclear because there is very little data available on possible systemic toxicities which may result from these higher levels. No significant adverse effects were seen in the children with the highest absorption levels. Aside from a propensity for children with SID to exhibit measurable levels of the drug, there does not seem to be a pattern of underlying conditions to explain while some children absorb relatively higher doses than others. It is notable that the two highest blood levels seen in the study were in impetigo patients with small areas of diseased skin.

At this time, the review by CDER's biopharmaceutics team is not available. (b) (4)

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David C. Bostwick

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/s/

David Bostwick
5/11/2009 01:14:21 PM
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