

Retapamulin

A new topical antibiotic used for impetigo

by Phil Brummond, PharmD

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Retapamulin (Altabax®, GSK) ointment is a newly approved topical antibiotic used in the treatment of impetigo. Impetigo is a skin infection that occurs more frequently in children than in adults and can resolve on its own, with success rates in placebo arms of studies up to 52.1%.¹ The majority of these infections are caused by *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*). Current treatment options used for impetigo include topical antibiotics such as mupirocin and oral antibiotics such as cephalexin. Retapamulin ointment is another treatment option for impetigo that shows no cross-resistance to other antibiotic classes.

PHARMACOLOGY/PHARMACOKINETICS

The mechanism of action of retapamulin is different than other antibiotics in that it selectively inhibits bacterial protein synthesis at the bacterial ribosome on the 50S subunit.² This interaction at the binding site allows for the inhibition of peptidyl transfer, the blocking of P-site interactions, and prevents active 50S ribosomal subunits from forming. The inhibition of protein synthesis results in the inability of bacterial cells to sustain life. This bacteriostatic antibiotic has shown efficacy at minimum inhibitory concentrations (MIC) against *S. aureus* and *S. pyogenes* and bactericidal properties at 1,000 times the MIC. Retapamulin has low systemic absorption, low oral bioavailability and is metabolized through the liver (CYP3A4) which makes it appropriate for topical administration.^{2,4} It is approximately 94% plasma protein bound, independent of concentration, with an unknown volume of distribution in humans.²

CLINICAL TRIALS

Impetigo

Oranje et al performed a randomized, double blind, placebo controlled trial comparing retapamulin to placebo for the treatment of impetigo in 17 centers across four countries.¹ Two hundred and ten patients, age 9 months to 73 years, were evaluated. Clinical success was evaluated seven days after the initiation of therapy. The retapamulin group showed a significantly greater success rate than the placebo group. Bacterial success rates were also statistically higher in the retapamulin group than in the placebo group with success rate treatment differences of 35.5% for *S. aureus* and 50.7% for *S. pyogenes* ($p < 0.0001$). The results of the study are summarized in Table 1.

Oranje et al also conducted a randomized, observer-blinded, noninferiority study comparing treatment courses of topical

Summary

Indications. Retapamulin is a pleuromutilin topical antibiotic approved for the treatment of impetigo (*S. aureus*; methicillin-susceptible only or *S. pyogenes*) in patients greater than 9 months of age.

Dose. Retapamulin is supplied in 5 gm, 10 gm and 15 gm tubes, and is dosed by applying a thin layer of ointment on the affected area twice daily for five days.

Pediatrics. Retapamulin is safe and effective in the treatment of impetigo in patients 9 months to 17 years of age.

Geriatrics. Retapamulin was studied in 234 patients greater than 65 years of age and there were no differences in effectiveness or safety when comparing these patients to patients less than 65 years of age.

Pregnancy. Category B

Breast Feeding. The safe use of retapamulin in nursing mothers has not been established. It is unknown whether there is excretion of retapamulin in human milk.

Elimination. Due to the low systemic absorption of topically applied retapamulin, the elimination has not been studied. In vitro studies have found cytochrome P450 3A4 (CYP3A4) is responsible for retapamulin's metabolism.

Administration. Retapamulin is administered topically to the affected area (up to 100 cm² in total area in adults or 2% total body surface area in pediatric patients >9 months of age).

Cost. \$88.78 AWP for 15 gm tube.

retapamulin to sodium fusidate ointment for the treatment of impetigo.³ Three hundred forty-five patients received retapamulin and one hundred seventy-two received sodium fusidate (2:1). The study was conducted in nine countries: Canada, Costa Rica, France, Germany, India, The Netherlands, Peru, Poland and South Africa. The primary endpoint was clinical response at the end of therapy (seven and nine days after initiation of therapy for retapamulin and sodium fusidate respectively) defined as success if lesions were absent, if lesions became dry without crusting, or if lesions decreased in size compared to baseline so no antimicrobial therapy was needed. Clinical failure was defined as insufficient improvement where additional antibiotic therapy was required to treat infection. The secondary endpoints were assessed at the end of therapy and at follow up (14 days after initiation of therapy) by measuring bacteriological responses. Patients were excluded if they had an underlying skin disease, a bacterial skin infection or systemic infection requiring oral or intravenous antibiotics.

The two study groups were similar in demographic and disease characteristics at baseline. Study participants ranged from 9 months to 84 years of age with a median age of nine in the retapamulin group and seven in the sodium fusidate group. Treatment adherence, defined as applying 80% of the prescribed doses, differed between study groups with 0.3% of patients in retapamulin and 4.1% in sodium fusidate being non-adherent ($p = 0.003$). The retapamulin group had a clinical success rate



similar to the sodium fusidate group. In all study populations statistical noninferiority was achieved. Retapamulin achieved statistical superiority in the bacteriology study population ($p=0.002$). Clinical and bacteriologic cure rates are summarized in Table 2.

Secondarily Infected Traumatic Lesions (SITL)

Free et al performed two identical, randomized, double blind, double-dummy, noninferiority, multicenter studies comparing the efficacy and safety of retapamulin and oral cephalexin for the treatment of SITL.⁴ Nineteen hundred and forty-one patients were randomized in the two studies. The clinical success rates at follow-up (days 12-14, retapamulin; days 17-19, cephalexin) in the per-protocol population were the studies' primary endpoints. Patients were included in the study if they had a SITL including abrasions, small lacerations, or a sutured wound. Patients were excluded if they had any hypersensitivities to β -lactam antibiotics or pleuromutilins. Patients were also excluded if they had symptoms of a systemic infection, an infection unlikely to contain *S. aureus* and/or *S. pyogenes*, or use of systemic antibiotics or steroids within 24 hours of starting the trial.

There was no difference in baseline demographic characteristics in either study when comparing the two treatment groups.

Overall, 89.5% of patients in the retapamulin group showed clinical success compared to 91.9% in the cephalexin group. Presumed microbiologic success was seen in 89.2% of patients that were treated with retapamulin compared to 90.2% in the cephalexin group. These results were similar in the intent to treat population. The trials demonstrated that retapamulin ointment was comparable to oral cephalexin for the treatment of SITL. Clinical and bacteriologic cure rates by study are summarized in Table 3.

Secondarily Infected Dermatitis (SID)

Parish et al conducted a randomized, double-blind noninferiority trial comparing retapamulin with an oral placebo to oral cephalexin with a placebo ointment in 11 countries in North America, Europe, Africa and Asia. Five hundred forty-seven patients greater than nine months of age were enrolled.⁵ Noninferiority treatment of SID was concluded if there was a treatment difference where the lower limit of the confidence interval was greater than or equal to -10%. (CI: -9.9) The clearing of all signs and symptoms of infection so that no additional antibiotic therapy was needed was defined as clinical success. Patients who had atopic dermatitis, psoriasis, or allergic contact dermatitis with

TABLE 1. CLINICAL AND BACTERIOLOGIC CURE OF IMPETIGO COMPARING RETAPAMULIN TO PLACEBO¹

	CLINICAL CURE		BACTERIOLOGIC CURE	
	Retapamulin (EOT/FU)	Placebo (EOT/FU)	Retapamulin (EOT/FU)	Placebo (EOT/FU)
PPC	89.5%/82.4%	53.2%/43.1%	89.7%/84.3%	50.0%/37.5%
ITT	85.6%/75.5%	52.1%/39.4%	88.6%/79.8%	49.1%/33.3%

PPC=per protocol; ITT=intent to treat; EOT=End of Therapy; FU=Follow up

TABLE 2. CLINICAL AND BACTERIOLOGIC CURE OF IMPETIGO COMPARING RETAPAMULIN TO SODIUM FUSIDATE³

	CLINICAL CURE		BACTERIOLOGIC CURE	
	Retapamulin (EOT/FU)	Sodium Fusidate (EOT/FU)	Retapamulin (EOT/FU)	Sodium Fusidate (EOT/FU)
PPC	99.1%/96.4%	94.0%/93.7%	99.2%/96.6%	93.0%/92.5%
ITT	94.8%/89.9%	90.1%/87.2%	95.1%/90.1%	88.5%/84.7%

PPC=per protocol; ITT=intent to treat; EOT=End of Therapy; FU=Follow up

TABLE 3. CLINICAL AND BACTERIOLOGIC CURE OF SITL AT FOLLOW UP COMPARING RETAPAMULIN TO CEPHALEXIN⁴

	CLINICAL CURE AT FOLLOW UP		BACTERIOLOGIC CURE AT FOLLOW UP	
	Retapamulin (Study A/ Study B)	Cephalexin (Study A/ Study B)	Retapamulin (Study A/ Study B)	Cephalexin (Study A/ Study B)
PPC	88.7%/90.4%	91.9%/92.0%	87.1%/91.7%	89.4%/91.1%
ITT	85.2%/87.5%	84.0%/87.4%	Not Reported	Not Reported

PPC=per protocol; ITT=intent to treat

TABLE 4. CLINICAL AND BACTERIOLOGIC CURE OF SID COMPARING RETAPAMULIN TO CEPHALEXIN⁵

	CLINICAL CURE		BACTERIOLOGIC CURE	
	Retapamulin (EOT/FU)	Cephalexin (EOT/FU)	Retapamulin (EOT/FU)	Cephalexin (EOT/FU)
PPC	92.0%/85.9%	93.8%/89.7%	93.0%/87.2%	94.1%/91.8%
ITT	92.3%/82.9%	91.8%/86.3%	93.4%/83.5%	91.3%/87.8%

PPC=per protocol; ITT=intent to treat; EOT=End of Therapy; FU=Follow up

signs or symptoms of a secondary infection were included in the study. Patients were excluded if they had hypersensitivities to one of the study agents, if causative bacteria were not suggestive of *S. aureus* or *S. pyogenes*, or if the patient received corticosteroids or antibiotics within 72 hours of starting the study.

Both treatment groups had similar demographic characteristics at baseline. Efficacy in the per-protocol patients was determined at end of therapy (days 7-9, retapamulin; days 12-14, cephalexin) and at follow up (days 12-14, retapamulin; days 17-19, cephalexin). Retapamulin was considered noninferior to cephalexin in all treatment comparisons. The secondary endpoint of microbiologic response was also similar between the two treatment groups. At the follow up visit, patients were asked about preference of oral versus topical therapy; 60.6% of patients using retapamulin and 56.8% of patients taking cephalexin preferred topical therapy. Clinical and bacteriologic cure rates are summarized in Table 4.

Two posters at the 45th Interscience Conference of Antimicrobial Agents and Chemotherapy presented the results of evaluations of retapamulin *in vitro* activity against MRSA and multi-drug resistant *S. aureus* skin infections.^{6,7} Isolates of *S. aureus* were collected from 53 sites in 13 countries and were tested and confirmed for methicillin resistance. Resistance was found in 32.9% (649) of the examined isolates. The MIC was determined to be 0.12 mcg/mL in the studied MRSA isolates.⁶ The results show promise that retapamulin has potential *in vitro* activity against MRSA; however, more studies are needed to evaluate clinical efficacy. (See Table 5)

CONTRAINDICATIONS/PRECAUTIONS/WARNINGS

There are no contraindications for the use of retapamulin. The precautions and warnings are similar to other topical antibiotics, including local irritation and potential for microbial overgrowth. Retapamulin is classified as pregnancy category B; however, there have been no adequate human studies in this patient population.²

DRUG INTERACTIONS

Co-administration of retapamulin and oral ketoconazole 200mg twice daily resulted in an increased area under the curve (AUC) and an 81% increase in maximum concentration of retapamulin.² These increases are not likely to be significant because of the low systemic absorption of retapamulin. Agents that are metabolized by CYP3A4 are also unlikely to be affected by topical administration of retapamulin. Retapamulin use with concurrent administration of multiple topical products has not been studied.

TABLE 5. CLINICAL SUCCESS RATES AT FOLLOW UP FOR PATIENTS WITH MRSA SKIN INFECTIONS THAT WERE TREATED WITH RETAPAMULIN.^{3,4,5}

Study	Retapamulin, n/N	Success Rate
Oranje et al ³	8/8	100%
Free et al ⁴	35/51	68.6%
Parish et al ⁵	5/5	100%

n/N= number of patients with positive clinical outcome/ total number of patients identified as having MRSA

ADVERSE EVENTS

In the clinical studies reviewed, the adverse events were mild to moderate in severity.^{1,3,4,5} In the study by Parish et al, adverse events were reported by 22% of patients receiving retapamulin and 22% of patients receiving cephalexin; however, the number of adverse events specifically related to treatment were low.⁵ Frequently reported adverse events in the retapamulin group were nasopharyngitis (3%) and headache (2%), and in the cephalexin group were nasopharyngitis (3%) and diarrhea (3%). Treatment-related adverse effects experienced within the retapamulin group were application site irritation (1%); application site pruritus (1%); and application site pain (<1%).

In the study conducted by Free et al, adverse events were reported in 5.3% of patients using retapamulin and 7.7% in the cephalexin group.⁴ The most common adverse event in the retapamulin group was application site irritation (1.3%), while diarrhea (1.9%) and nausea (1.6%) were the most commonly reported adverse events in the cephalexin group. Discontinuation of therapy occurred as a result of an adverse event in 1.9% of the patients using retapamulin and 2.2% of patients taking cephalexin.

Phase 3 clinical trials reported by the manufacturer demonstrated adverse events similar to the clinical trials published in the literature. (See Table 6) Other adverse events that occurred in phase 3 trials were nausea (1.2%), increases in creatinine phosphokinase (<1%), pruritus (1.5%), eczema (1%), pyrexia (1.2%), application site pain (<1%), erythema (<1%), and contact dermatitis (<1%).²

COST, DOSE AND HOW SUPPLIED

Retapamulin is supplied in 5 gm, 10 gm and 15 gm tubes, and is dosed by applying a thin layer of ointment on the affected area

TABLE 6. ADVERSE EVENTS REPORTED IN ADULT AND PEDIATRIC PATIENTS TREATED WITH RETAPAMULIN IN PHASE 3 CLINICAL TRIALS²

Adverse Event	Retapamulin (Adults) n=1,527 %	Retapamulin (Pediatrics) n=588 %	Cephalexin (Adults) n=698 %	Cephalexin (Pediatrics) n=121 %
Application site irritation	1.6	1.9	<1	0
Diarrhea	1.4	1.7	2.3	5
Nasopharyngitis	1.2	1.5	<1	1.7
Headache	2	1.2	2	1.7

TABLE 7. DRUG THERAPY COST COMPARISON FOR IMPETIGO

Drug Name	Package Size	AWP cost per treatment
Retapamulin (Altabax [®])	15 gm	\$88.78
Mupirocin	22 gm	\$44.65
Bacitracin	30 gm	\$3.12
Cephalexin 250 mg/5mL (Pediatrics: 25-50 mg/kg/day orally divided every six hours)	100 mL	\$18.90

twice daily for five days.² Treatment costs are outlined in Table 7. These data are based on the estimated cost to treat a patient per episode of impetigo.

CONCLUSION

Retapamulin offers a new mechanism of action and should be considered as an alternative for the treatment of impetigo. First line therapies (i.e., mupirocin, bacitracin and cephalexin) provide coverage of most bacteria commonly found in impetigo. While some abstracts and studies have shown *in vitro* activity of retapamulin against MRSA, additional studies are needed to assess clinical efficacy.^{3,4,5,6,7} For most patients, the high cost of retapamulin is not justified, as advantages over alternative therapies have not been shown. ●

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Health Mart Wellness Tour Hits 20 Wisconsin Cities



As part of Health Mart's Mobile Wellness Tour, a Health Mart-branded RV visited 20 Wisconsin communities in March and April to provide free blood pressure, bone density, cholesterol and diabetes screenings.

Among the pharmacies participating in the screenings was Edgerton Health Mart Pharmacy, owned and operated by Eric and Jenna Gresens. The bus rolled into Edgerton on a snowy March 27. While the poor weather led to a lower than expected turn-out, Jenna Gresens reports that pharmacy staff referred 20 patients to the Health Mart bus for screenings during the three-hour shift.