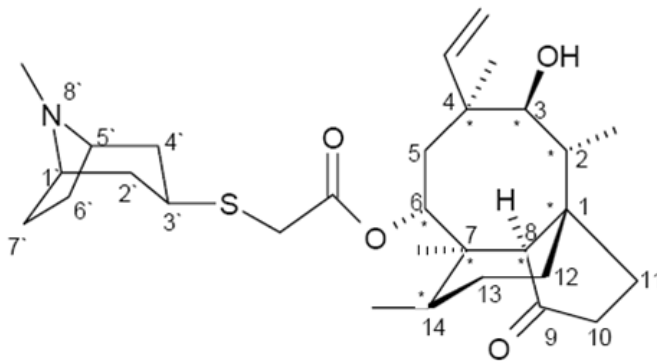


ALTARGO[®]
PRODUCT INFORMATION

NAME OF THE MEDICINE

Retapamulin

Structure:



CAS Number: 224452-66-8

DESCRIPTION

Retapamulin is a white to pale yellow solid with a molecular weight of 517.78. The partition coefficient (log D) of retapamulin in octanol and water is +1.89.

Altargo is an off-white, smooth ointment for topical use which contains the active ingredient retapamulin 1% w/w. Altargo also contains the inactive ingredient soft white paraffin and may contain traces of the antioxidant, butylated hydroxytoluene.

PHARMACOLOGY

Pharmacodynamics:

Mechanism of Action

Retapamulin is a semisynthetic derivative of the compound pleuromutilin, which is isolated through fermentation from *Clitopilus passeckerianus*.

Retapamulin selectively inhibits bacterial protein synthesis by interacting with the 50S subunit of the bacterial ribosome in a way that is distinct from that of other non-pleuromutilin antibiotics that interact with the ribosome.

Data indicate that the binding site involves ribosomal protein L3 and is in the region of the ribosomal P site and peptidyl transferase centre. By virtue of binding to this site, pleuromutilins inhibit peptidyl transfer, partially block P-site interactions, and prevent normal formation of active 50S ribosomal subunits, and therefore appear to inhibit bacterial protein synthesis by multiple mechanisms.

Due to this distinct mode of action, *in vitro* target-specific cross-resistance with retapamulin and other classes of antibiotics is rare.

Pharmacodynamic Effects

Retapamulin is active against most isolates of the common skin and skin structure pathogens *Staphylococcus aureus* and *Streptococcus pyogenes*, both *in vitro* and in clinical studies. However, retapamulin has limited activity against some MRSA strains in the clinical setting (see *Clinical Trials*).

It also has *in vitro* activity against some other Gram-positive, Gram-negative and anaerobic bacteria.

Retapamulin is predominantly bacteriostatic against *S. aureus* and *S. pyogenes*. The minimum bactericidal concentration (MBC) against *S. aureus* and *S. pyogenes* was 512 to 1024 fold higher than the minimum inhibitory concentration (MIC).

The following *in vitro* data are available, but their clinical significance is unknown: Retapamulin is active against most isolates of *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *viridans streptococci*, *Propionibacterium acnes*, *Peptostreptococcus* species, *Prevotella* species, *Fusobacterium* species and *Porphyromonas* species.

Resistance

Due to the distinct mode of action, *in vitro* target specific cross-resistance with retapamulin and other classes of antibiotics is rare.

A reduction in the *in vitro* activity of pleuromutilins is mediated through mutations in ribosomal protein L3. The presence of the ABC transporter *vgaAv* reduces the *in vitro* activity of retapamulin. Susceptibility to pleuromutilins can also be affected by the Cfr rRNA methyltransferase, which confers cross-resistance to phenicols, lincosamides and streptogramin A in staphylococci.

Retapamulin has shown a low potential for development of resistance *in vitro*. The highest retapamulin MIC from serial passage of *S. aureus* and *S. pyogenes* in the presence of sub-minimum inhibitory concentrations (sub-MICs) of retapamulin was 2 micrograms/ml. No development of resistance was observed during treatment with retapamulin in the retapamulin clinical study programme.

The prevalence of retapamulin resistance may vary geographically and with time for selected species. Local recommendations about antibiotic use and prevalence of resistance should be taken into consideration.

Pharmacokinetics:

Absorption

In a study of healthy adult subjects, retapamulin ointment, 1%, was applied daily to intact and to abraded skin under occlusion for up to 7 days. Systemic exposure following topical application of retapamulin through intact skin was very low. The geometric mean C_{max} value in plasma after application to 200 cm² of abraded skin was 9.75 ng/ml on day 1 and 8.79 ng/ml on day 7. The maximum individual systemic exposure (C_{max}) after a single topical application of retapamulin ointment, 1%, to 200 cm² of abraded skin, was 22.1 ng/ml.

Plasma samples were obtained from 516 adult and paediatric patients who were receiving topical treatment with retapamulin twice daily for the treatment of secondarily infected traumatic lesions. The majority of samples (89%) were below the lower limit of quantitation (lower limit of quantitation 0.5ng/ml). Of the remaining samples which had measurable concentrations (11%), the majority (90%) had retapamulin concentrations less than 2.5ng/ml. The maximum measured retapamulin concentration in adults was 10.7ng/ml and in paediatric patients (aged 2-17 years) was 18.5ng/ml.

Children up to 2 years of age

In a paediatric study assessing the pharmacokinetics of topical retapamulin, plasma samples were obtained from patients aged 2 months to 2 years. Forty-six percent of samples had measurable retapamulin concentrations (range 0.52 to 177.3 ng/ml), with the majority (75%) having concentrations <5.0 ng/ml.

2 months to 9 months

Plasma concentrations of retapamulin were measurable in 69% of patients (n = 20). Four plasma retapamulin concentrations in this age group (26.9, 80.3, 174.3, and 177.3 ng/ml) were higher than the highest observed retapamulin level seen in paediatric patients aged 2-17 years (18.5ng/ml). Retapamulin is not indicated in paediatric patients less than 9 months of age (see *Dosage and Administration*).

9 months to 2 years

Plasma concentrations of retapamulin were measurable in 32% of patients (n = 16). One plasma retapamulin concentration in this age group (95.1 ng/ml) was higher than the highest observed retapamulin level seen in paediatric patients aged 2-17 years (18.5ng/ml) (see *Interactions*).

Co-administration with ketoconazole

Co-administration of oral ketoconazole 200mg twice daily increased mean retapamulin AUC(0-24) and C_{max} by 81% after topical application of retapamulin 1% ointment on the abraded skin of healthy adult males.

Co-administration of retapamulin and CYP3A4 inhibitors such as ketoconazole, has not been studied in children.

Due to low systemic exposure following topical application in adults and paediatric patients 2 years of age and older, dosage adjustments for retapamulin are unnecessary in these patients when co-administered with CYP3A4 inhibitors. For children less than 2 years of age (see *Interactions*).

Distribution

Tissue distribution of retapamulin has not been investigated in humans.

Retapamulin is approximately 94% bound to human plasma proteins.

Metabolism

Retapamulin metabolism in humans was investigated using non-quantitative methodologies only. Two minor mono-oxygenated metabolites were detected in plasma of healthy subjects. Metabolites found in urine included two N-demethylated metabolites and numerous products of mono-oxygenation as well as further oxidation products.

In *in vitro* human hepatocyte studies, the main routes of metabolism were mono-oxygenation and di-oxygenation. The major enzyme responsible for metabolism of retapamulin in human liver microsomes is CYP3A4. In freshly excised human skin, very low amounts of three mono-oxygenated metabolites were generated.

Excretion

Retapamulin excretion in humans has not been investigated.

CLINICAL TRIALS

Impetigo

The efficacy of topical retapamulin ointment (applied twice daily for five days) for the treatment of primary impetigo (with lesions not larger than 100cm² in total area) was evaluated in two clinical trials. Study number TOC103469 was a randomised (2:1), double blind clinical trial compared to topical placebo ointment; Study number TOC100224 was a randomised, (2:1) observer blind clinical trial compared to topical sodium fusidate ointment, 2%. For both clinical trials, the primary endpoint was clinical response at end of therapy (2 days post-treatment). A total of 727 patients were enrolled in these studies. In Study 103469, clinical efficacy rates in the primary population (intent to treat population - ITT) were 85.6% for retapamulin and 52.1% for placebo (95% CI 20.5%, 46.5% for treatment difference)); the microbiological success rate was 91.2% for retapamulin and 50.9% for placebo. This study demonstrated topical retapamulin to be superior to placebo ointment.

In study TOC100224, clinical efficacy rates in the primary population (per protocol population – PPP) were 99.1% for retapamulin and 94.0% for sodium fusidate ointment (95% CI 1.1%, 9.0% for treatment difference)); the microbiological success rate was 98.3% for retapamulin and 93.9% for sodium fusidate ointment. In this study, topical retapamulin demonstrated non-inferiority to sodium fusidate.

Secondarily infected traumatic lesions

The efficacy of topical retapamulin 1% ointment (applied twice daily for five days) for the treatment of secondarily infected traumatic skin lesions (e.g. lacerations, sutured wounds and abrasions not more than 10cm in length or 100cm² in total area) was compared to that of oral cephalexin (500mg twice daily for 10 days for adults and adolescents, and 12.5mg/kg twice daily for paediatric patients less than 13 years of age) in two randomized (2:1), double-blind, double-dummy clinical trials. A total of 1904 patients were enrolled in these two studies. The primary endpoint was clinical response in the per protocol population at 7-9 days post-treatment. In the first study (Study number 030A), clinical efficacy was 88.7% for retapamulin and 91.9% for cephalexin (95% CI -7.4%, 0.9% for treatment difference). In the second study (Study number 030B), clinical efficacy was 90.4% for retapamulin and 92.0% for cephalexin (95% CI -5.8, 2.6% for treatment difference). Microbiological success rate at follow-up in the per-protocol populations was 87.1% for retapamulin and 89.4% for cephalexin in the first study and 91.7% for retapamulin and 91.1% for cephalexin in the second study. In these studies, topical retapamulin demonstrated non-inferiority to oral cephalexin.

A further study (TOC110977) was conducted in subjects with SITL using a placebo control. A total of 508 subjects were enrolled in this study. The study was a randomized, double-blind, placebo-controlled, superiority study in subjects ³ 2 months of age with SITL. The study failed to meet the primary endpoint which was the clinical response (success or failure) at follow-up (day 12 to 14). The difference in the clinical success rates (8.4%) at the follow-up visit between subjects treated with retapamulin (74.8%) and placebo (66.4%) was not statistically significant (ITTC Primary Efficacy Population, 95% CI -1.6, 18.4).

Using logistic regression analysis to adjust for the differences in baseline wound characteristics, for the primary endpoint, the retapamulin treatment was found to be superior to placebo (p=0.0336) with an odds ratio estimate of 1.73 and 95% CI of (1.04, 2.87).

The clinical response in bacteriologically confirmed subjects (ITTB population) was a secondary efficacy endpoint. Retapamulin was statistically superior to placebo in the ITTB population (76.4% versus 64.3%).

Secondarily infected dermatoses

The efficacy of topical retapamulin ointment, 1% (applied twice daily for five days) for the treatment of secondarily-infected dermatoses (e.g. atopic dermatitis, psoriasis, and allergic contact dermatitis with lesions not larger than 100cm²) was compared to that of oral cephalexin (500mg twice daily for 10 days for adults and adolescents, and 12.5mg/kg twice daily for paediatric patients less than 13 years of age) in a randomized (2:1), double-blind, double-dummy clinical trial (Study number 032). A total of 546 patients were enrolled in this study. Clinical efficacy rates at follow-up in the per-protocol populations were 85.9% for retapamulin and 89.7% for cephalexin (95% CI -9.9%, 2.3% for treatment difference). Microbiological success rate at follow-up in the per-protocol populations was 85.0% for retapamulin and 90.8% for cephalexin. In this study, topical retapamulin demonstrated non-inferiority to oral cephalexin.

Methicillin-resistant Staphylococcus aureus

Clinical experience in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection is limited. In studies of secondarily infected traumatic lesions, lower clinical efficacy was demonstrated with retapamulin than with oral cephalexin against some MRSA strains.

A study was conducted in subjects with SITL or impetigo to evaluate the efficacy and safety of retapamulin versus linezolid in subjects with MRSA (Study TOC110978). A total of 410 subjects were enrolled in this study. The study was a randomized, double-blind, double-dummy study of retapamulin ointment versus oral linezolid in subjects ³ 2 months of age with SITL or impetigo due to MRSA. The primary endpoint was the clinical response (success or failure) at follow-up (day 12-14 for retapamulin and day 17-19 for linezolid) in the per-protocol MRSA (PPMRSA) population.

Retapamulin had a significantly lower clinical success rate than linezolid in this study when response is defined as clinical success only. Clinical success at follow-up in the PPMRSA group was 63.9% (95% CI: 51.9, 76.0) in the retapamulin group and 90.6% (95% CI: 80.5, 100.7) in the linezolid group.

Paediatric patients

1141 patients aged less than 18 years, 740 of whom received at least one dose of retapamulin ointment were included in the phase III clinical studies for secondarily infected

dermatoses, secondarily infected traumatic lesions and primary impetigo (ITTC population). There was no difference in efficacy between adult and paediatric patients.

INDICATIONS

Altargo is indicated for the short term treatment of superficial skin infections (including impetigo, infected small lacerations, abrasions, sutured wounds, and secondarily infected dermatoses) in adults, adolescents, children and infants aged from 9 months, in the absence of abscess formation and infections due to MRSA.

The *in vitro* susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.

CONTRAINDICATIONS

Retapamulin ointment is contraindicated in patients with a known or suspected hypersensitivity to retapamulin or any component of the ointment.

PRECAUTIONS

Patients should be frequently assessed for non-responsiveness or progression of infection. If this occurs, change to a systemic antimicrobial agent may be necessary.

Retapamulin may be less effective than an appropriate oral agent for the treatment of superficial skin infections caused by MRSA.

Retapamulin should not be used to treat abscesses.

In the event of a sensitisation or severe local irritation from the use of retapamulin ointment, treatment should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted.

Do not use in the eyes. Retapamulin has not been evaluated for ophthalmic use.

Do not use on mucous membranes. The safety and efficacy of retapamulin on mucosal surfaces have not been established. Epistaxis has been reported with use of retapamulin on nasal mucosa.

Do not ingest.

As with other antibacterial agents, prolonged use may result in overgrowth of non-susceptible microorganisms, including fungi.

Effects on Fertility:

No treatment-related effects on male or female fertility have been shown in animal studies.

No evidence of impaired fertility was found in male or female rats given retapamulin 50, 150, or 450 mg/kg/day orally.

Use in Pregnancy (Category B3):

There is no adequate experience with retapamulin in human pregnancy.

Animal studies have shown minor effects on foetal growth and incomplete ossification after oral administration, and have not been evaluated with respect to effects on postnatal development.

Retapamulin ointment should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Effects on embryo-foetal development were assessed in pregnant rats given 50, 150, or 450 mg/kg/day by oral gavage on days 6 to 17 postcoitus. Maternal toxicity (decreased body weight gain and food consumption) and developmental toxicity (decreased foetal body weight and delayed skeletal ossification) were evident at doses ≥ 150 mg/kg/day (yielding dose ratios on a mg/m^2 basis ≥ 136 - times the estimated clinical dose). There were no treatment-related malformations observed in foetal rats.

Retapamulin was given as a continuous intravenous infusion to pregnant rabbits at dosages of 2.4, 7.2 or 24 mg/kg/day from day 7 to 19 of gestation. Maternal toxicity (reduced body weight gain, food consumption and abortions) was demonstrated at dosages ≥ 7.2 mg/kg/day (8-fold higher than the estimated human systemic exposure (AUC; 238 ng.h/ml). There was no treatment-related effect on embryo-foetal development.

Use in Lactation:

The safe use of retapamulin during lactation has not been established.

Paediatric Use:

The safety and efficacy of retapamulin ointment has not been established in paediatric patients less than nine months of age.

Use in the Elderly:

No dosage adjustment necessary.

Carcinogenicity:

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with retapamulin.

Genotoxicity:

Retapamulin showed no genotoxicity when evaluated *in vitro* for gene mutation and/or chromosomal effects in the mouse lymphoma cell assay, in cultured human peripheral blood lymphocytes, or when evaluated *in vivo* for chromosomal effects in a rat micronucleus test.

Ability to perform tasks that require judgement, motor or cognitive skills:

No detrimental effects on such activities are predicted from the pharmacology or adverse reaction profile of this medicinal product.

INTERACTIONS WITH OTHER MEDICINES

No clinically significant drug interactions are known in adults (see *Pharmacokinetics*).

No drug interaction studies have been conducted in children. In children under two years of age, increased systemic exposure to retapamulin has been observed. As CYP3A4 inhibitors may further increase systemic exposure to retapamulin, caution should be exercised if CYP3A4 inhibitor(s) are used concomitantly with retapamulin in young children. (see *Pharmacokinetics*)

The effect of concurrent application of retapamulin and other topical products to the same area of skin has not been studied, and is not recommended.

ADVERSE EFFECTS

Most Frequently Reported Adverse Events in Subjects with SITL/SID or Impetigo from the phase III studies (%)

Preferred Term	Retapamulin	Linezolid	Cephalexin	Fusidic Acid	Placebo
<i>Impetigo</i>	(N=563)	(N=46)	(N=0)	(N=172)	(N=71)
Any event	21.14	23.91	-	14.35	25.35
Application site pruritus	2.66	0	-	0	1.41
Headache	1.95	2.17	-	0	0
Application site pain	1.78	0	-	0	0
Pyrexia	1.07	0	-	0	1.41
Diarrhoea	0.789	6.52	-	1.16	0
Impetigo	0.53	0	-	0	2.82
Excoriation	0.36	0	-	2.33	0
Nausea	0.18	4.35	-	0	0
Arthropod bite	0	0	-	1.16	0
Xerosis	0	0	-	0	2.82
Urinary tract infection	0	0	-	2.33	0
<i>SITL/SID</i>	(N=2161)	(N=91)	(N=819)	(N=0)	(N=165)
Any event	19.81	34.07	25.03	-	4.85
Diarrhoea	1.57	14.29	2.69	-	0
Application site pain	1.48	0	0.49	-	0
Headache	1.39	5.49	1.95	-	0
Nasopharyngitis	1.30	0	0.85	-	0
Nausea	1.11	8.79	1.83	-	0.61
Pyrexia	0.42	1.10	0.37	-	1.82
Abdominal discomfort	0.28	2.20	0.37	-	0
Abdominal distension	0	2.20	0.12	-	0

Most Frequently Reported Drug-Related Adverse Events in Decreasing Frequency from the phase III studies (%)*

Preferred Term	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)
Any event	5.36	18.25	6.59	0.58	0.85
Diarrhoea	0.88	8.03	1.71	0	0
Application site pain	1.54	0	0.49	0	0
Nausea	0.59	5.84	1.22	0	0
Application site pruritus	0.84	0.73	0.37	0	0.42
Headache	0.26	2.19	0.24	0	0
Abdominal discomfort	0.18	1.46	0	0	0
Dysgeusia	0	1.46	0	0	0

* Causality was determined by the investigator to be drug related

Data from large clinical trials were used to determine the frequency of adverse reactions. The following convention has been used for the classification of frequency:

- Very common $\geq 1/10$
- Common $\geq 1/100$ and $< 1/10$
- Uncommon $\geq 1/1000$ and $< 1/100$
- Rare $\geq 1/10,000$ and $< 1/1000$
- Very rare $< 1/10,000$.

Clinical Trial Data:

General disorders and administration site conditions

Common: Application site reactions: irritation

Uncommon: Application site reactions: pruritus, pain, erythema

Skin and subcutaneous tissue disorders

Uncommon: Contact dermatitis

Postmarketing Data:

Immune System Disorders

Unknown: Hypersensitivity, including angioedema

General disorders and administration site conditions

Unknown: Application site irritation (including burning)

DOSAGE AND ADMINISTRATION

Adults, adolescents, children, and infants aged nine months and over

A thin layer of ointment should be applied to the affected area twice daily for five days. The area treated may be covered with sterile bandage or gauze dressing if desired. Patients not showing a clinical response within three to four days should be re-evaluated.

Safety and efficacy has not been established in secondarily infected traumatic lesions more than 10cm in length or 100cm² in surface area, or in secondarily infected dermatoses or primary impetigo affecting more than 100cm² in surface area (or exceeding 2% of body surface area in paediatric patients).

For topical application only.

Populations

Infants under nine months of age

The safety and efficacy of retapamulin ointment has not been established in paediatric patients less than nine months of age.

Elderly

No dosage adjustment necessary.

Renal impairment

No dosage adjustment is necessary. In view of the low systemic exposure to retapamulin following topical application, renal impairment is not expected to result in systemic exposure of clinical concern (see *Pharmacokinetics*).

Hepatic impairment

No dosage adjustment is necessary. In view of the low systemic exposure to retapamulin following topical application, hepatic impairment is not expected to result in systemic exposure of clinical concern (see *Pharmacokinetics*).

OVERDOSAGE

Symptoms and Signs

There is no experience with overdosage of retapamulin.

Treatment

Any signs or symptoms of overdosage, either topically or by accidental ingestion, should be treated symptomatically.

No specific antidote is known.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Attachment 1: Product information for AusPAR Retapamulin; Altargo; GlaxoSmithKline Australia Pty Ltd; PM-2012-01489-3-2 Date of Finalisation 11 November 2013. This Product Information was approved at the time this AusPAR was published.

PRESENTATION AND STORAGE CONDITIONS

Altargo is an off-white, smooth ointment supplied in 2.5 g, 5 g, 10 g and 15 g aluminium tubes with a plastic screw cap.

Not all pack sizes may be distributed in Australia.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):

24 July 2013

ALTARGO[®] is a registered trade mark of the GlaxoSmithKline group of companies.

Version 1.0