For the use only of registered medical practitioners or a hospital or a laboratory

ALTARGO™

Retapamulin Ointment 1 %

QUALITATIVE AND QUANTITATIVE COMPOSITION

Retapamulin 10 mg per gram (1% w/w)

PHARMACEUTICAL FORM

Ointment.

CLINICAL PARTICULARS

Therapeutic Indications

ALTARGO is indicated for the topical treatment of the following bacterial skin and skin structure infections (SSSI):

- Primary impetigo

- Secondarily infected traumatic lesions e.g. small lacerations, abrasions, sutured wounds

- Secondarily infected dermatoses including infected psoriasis, infected atopic dermatitis and infected contact dermatitis

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

For a list of susceptible microorganisms see Pharmacodynamic Properties.

Posology and Method of Administration

Adults, 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).

**Route of Administration**

Topical.

**Populations**

- **Infants under nine months of age**

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

- **Elderly**

  No dosage adjustment is 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.

- **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.

**Contraindications**

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

**Special Warnings and Special Precautions for Use**

In the event of a sensitisation or severe local irritation from the use of ALTARGO ointment, treatment should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted.
Do not use in the eyes. ALTARGO has not been evaluated for ophthalmic use.

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

Do not ingest.

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

**Interaction with Other Medicaments and Other Forms of Interaction**

No clinically significant drug interactions are known in adults.

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 ALTARGO in young children.

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

**Pregnancy and Lactation**

There is no adequate experience with ALTARGO in human pregnancy. Animal studies have shown minor effects on foetal growth after oral administration, and have not been evaluated with respect to effects on postnatal development. ALTARGO ointment should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

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

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

**Effects on Ability to Drive and Use Machines**

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

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 ≥1/10
- Common ≥1/100 and <1/10
- Uncommon ≥1/1000 and <1/100
- Rare ≥1/10,000 and <1/1000
- Very rare <1/10,000

Clinical Trial Data

<table>
<thead>
<tr>
<th>General disorders and administration site conditions:</th>
<th>Application site reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>irritation</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>pruritus, pain, erythema</td>
</tr>
</tbody>
</table>

Skin and subcutaneous tissue disorders

Uncommon: contact dermatitis

Postmarketing Data

<table>
<thead>
<tr>
<th>Immune System Disorders:</th>
<th>Hypersensitivity, including angioedema</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions:</th>
<th>Application site irritation (including burning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown:</td>
<td></td>
</tr>
</tbody>
</table>

Unknown:
**Overdose**

There is no experience with overdosage of *ALTARGO*.

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

No specific antidote is known.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

**Microbiology**

**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 was less efficacious against some MRSA strains in the clinical setting.

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, lincosamindes 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.

**Pharmacokinetic Properties**

**Absorption**

In a study of healthy adult subjects, *ALTARGO* ointment, 1%, was applied daily to intact and to abraded skin under occlusion for up to 7 days. Systemic exposure following topical application of *ALTARGO* through intact skin was very low. The geometric mean $C_{\text{max}}$ value in plasma after application to 200 cm$^2$ of abraded skin was 9.75 ng/mL on day 1 and 8.79 ng/mL on day 7. The maximum individual systemic exposure ($C_{\text{max}}$) after a single topical application of *ALTARGO* ointment, 1%, to 200 cm$^2$ of abraded skin, was 22.1 ng/mL.

Plasma samples were obtained from 516 adult and paediatric patients who were receiving topical treatment with *ALTARGO* 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 ALTARGO, 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). ALTARGO is not indicated in paediatric patients less than 9 months of age (see Posology and Method of 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 Interaction with Other Medicaments and Other Forms of Interaction).

- **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 ALTARGO 1% ointment on the abraded skin of healthy adult males.

Co-administration of ALTARGO 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 ALTARGO are unnecessary in these patients when co-administered with CYP3A4 inhibitors.

For children less than 2 years of age, see Interaction with Other Medicaments and Other Forms of Interaction.
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.

Elimination

Retapamulin elimination in humans has not been investigated.

Special Patient Populations

No data.

Clinical Studies

- Secondarily infected traumatic lesions

The efficacy of topical ALTARGO 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 ALTARGO 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 ALTARGO 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 ALTARGO and 89.4% for cephalexin in the first study and
91.7% for ALTARGO and 91.1% for cephalexin in the second study. In these studies, topical ALTARGO demonstrated non-inferiority to oral cephalexin.

- **Secondarily infected dermatoses**

  The efficacy of topical ALTARGO 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 ALTARGO 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 ALTARGO and 90.8% for cephalexin. In this study, topical ALTARGO demonstrated non-inferiority to oral cephalexin.

- **Impetigo**

  The efficacy of topical ALTARGO 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 ALTARGO and 52.1% for placebo (95% CI 20.5%, 46.5% for treatment difference); the microbiological success rate was 91.2% for ALTARGO and 50.9% for placebo. This study demonstrated topical ALTARGO to be superior to placebo ointment.

  In study TOC103469, clinical efficacy rates in the primary population (per protocol population – PPP) were 99.1% for ALTARGO and 94.0% for sodium fusidate ointment (95% CI 1.1%, 9.0% for treatment difference); the microbiological success rate was 98.3% for ALTARGO and 93.9% for sodium fusidate ointment. In this study, topical ALTARGO demonstrated non-inferiority to sodium fusidate.
• 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 ALTARGO than with oral cephalexin against some MRSA strains.

Paediatric Patients

Eight hundred and ninety nine patients aged nine months to 17 years, 588 of whom received at least one dose of ALTARGO ointment, were included in the five pivotal clinical studies for secondarily infected dermatoses, secondarily infected traumatic lesions and primary impetigo. There was no difference in efficacy between adult and paediatric patients.

Preclinical Safety Data

Carcinogenesis, mutagenesis, impairment of fertility:

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

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.

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

Embryo-foetal development:

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. 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.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**

White soft paraffin

Butylated hydroxytoluene

**Incompatibilities**

None known.

**Shelf Life**

*Unopened:* 24 months

*In-use:* 7 days

The expiry date is indicated on the packaging.

**Special Precautions for Storage**

Store below 30°C.

Do not freeze

KEEP OUT OF REACH OF CHILDREN

**Nature and Specification of Container**

Aluminium tubes with a polyethylene or polypropylene cap.

All presentations may not be marketed in India.

**Instructions for Use / Handling**

No special requirements.
Manufactured by

Glaxo Operations UK Limited
(trading as Glaxo Wellcome Operations)
Harmire Road, Barnard Castle
Co. Durham DL12 8DT
United Kingdom

Imported by

GlaxoSmithKline Pharmaceuticals Ltd.,
S.No.14/4, Godown No 1 & 2, Village Yavai,
Dist Thane, Bhiwandi.

Marketed by

GlaxoSmithKline Pharmaceuticals Limited,
Dr. Annie Besant Road, Mumbai 400 030, India.

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