

# Retapamulin (Altargo): novel antibacterial for impetigo

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## KEY POINTS

- retapamulin (Altargo) is licensed for the treatment of impetigo and minor skin infection
- available as a 1 per cent ointment (5g = £7.89) applied twice daily for five days
- contraindicated in the treatment of abscesses and suspected MRSA infection
- is superior to placebo and noninferior to fusidic acid ointment 2 per cent in the treatment of impetigo, with clinical success rates of 86-95 per cent at the end of treatment and 76-90 per cent at follow-up after 14 days
- treatment is well tolerated, with application-site reactions the most frequently reported events in clinical trials
- retapamulin provides a useful option for treating fusidic acid-resistant impetigo



**Retapamulin is a new topical antibacterial licensed for impetigo and minor skin infections. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Cameron Kennedy comments on its place in therapy.**

Guidance on the treatment of minor skin infections is cautious about the use of topical antibiotics. In the case of impetigo, a topical antibiotic is indicated for small, localised lesions to eradicate infection, relieve symptoms and reduce the risk of transmission.

The drug of first-line choice is fusidic acid (Fucidin); mupirocin (Bactroban) should be reserved for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and more serious cases require oral therapy.<sup>1</sup> For uncomplicated minor wounds such as abrasions, there is no definitive guidance but cleaning with a topical antiseptic is preferred to a topical antibiotic as initial treatment.<sup>2</sup>

### The technology

Retapamulin (Altargo) is a novel antibacterial, the first of the pleuromutilins. It is bacteriostatic and,

like the macrolides, targets the bacterial 50S ribosome subunit, though at a different binding site.

In the UK, retapamulin is being promoted for the short-term treatment of impetigo<sup>3</sup> but it is also licensed for the treatment of superficial skin infections of small lacerations, abrasions or sutured wounds. Formulated as a 1 per cent ointment, it is applied twice daily for five days. Alternative treatment should be considered if there is no response within two to three days.

Efficacy has not been determined in very large or numerous lesions and retapamulin is contraindicated in the treatment of abscesses and in patients with suspected MRSA infection.

### Clinical trials

Retapamulin ointment 1 per cent has been compared with placebo (trial available only as an abstract)<sup>4</sup>

and fusidic acid ointment 2 per cent<sup>5</sup> in the treatment of impetigo. It has also been compared with oral cefalexin in the treatment of secondarily-infected traumatic skin lesions<sup>6</sup> – this choice of comparator does not reflect UK clinical practice and this study, which demonstrated no difference between treatments, is not considered further.

In the placebo-controlled study,<sup>4</sup> 213 patients with impetigo – 82 per cent with confirmed infection by *Staph. aureus* or *Streptococcus pyogenes* – and aged nine months to 73 years were randomised to treatment with retapamulin or placebo for five days. Clinical success rates (not defined) at seven days after starting treatment were 86 per cent with retapamulin and 52 per cent with placebo. Subgroup analyses also demonstrated significantly greater efficacy in patients aged

Analysis population	Retapamulin		Fusidic acid		Difference in success rates (%)	95% confidence limits	p value
	n	success rate (%)	n	success rate (%)			
clinical PP	314/317	99.1	141/150	94.0	5.1	1.1, 9.0	0.003
clinical ITT	327/345	94.8	155/172	90.1	4.7	-0.4, 9.7	0.062
bacteriology PP	240/242	99.2	106/114	93.0	6.2	1.4, 11.0	0.002
bacteriology ITT	250/263	95.1	116/131	88.5	6.5	0.5, 12.6	0.022

**Table 1.** End-of-therapy clinical response and bacteriological sample susceptibility for retapamulin versus fusidic acid, showing that retapamulin is non-inferior; PP = per protocol, ITT = intent to treat (after Oranje *et al*<sup>5</sup>)

under 18 and when stratified by pathogen.

Additional data available elsewhere show that the clinical response rates at follow-up after 14 days were 76 per cent for retapamulin and 36 per cent with placebo.<sup>7</sup>

The second trial was an observer-blind, noninferiority study – 519 patients, age nine months to 84 years, most of whom had a single impetigo lesion, were randomised to treatment with retapamulin twice daily for five days or fusidic acid three times daily for seven days.<sup>5</sup> The primary end-point was clinical success, *ie* complete resolution or improvement of the lesion such that no further antibiotic treatment was necessary, or failure, *ie* lesion worse, crusted or exudative and requiring further antibiotic treatment. End-points were assessed at the end of each treatment and at follow-up after 14 days.

At least one pathogen, mainly *Staph. aureus* or *Strep. pyogenes*, was isolated in 76 per cent of participants. The prevalence of MRSA was 2.9 per cent. Isolates resistant to fusidic acid occurred in 4.4 per cent of patients randomised to retapamulin and 8.0 per cent of those using fusidic acid.

By intent to treat analysis, end-of-therapy clinical success rates

were 95 per cent with retapamulin and 90 per cent with fusidic acid (see Table 1), demonstrating that retapamulin is noninferior. At follow-up, clinical success rates were 90 and 87 per cent respectively.

Bacteriological success rates were claimed to be high, but few patients had repeat cultures and eradication was inferred from clinical success. For *Staph. aureus* isolates resistant to fusidic acid, retapamulin was associated with clinical success against all nine isolates (though fusidic acid was nonetheless effective against four of seven isolates). There was no difference in efficacy against MRSA isolates and retapamulin was superior against mupirocin-resistant *Staph. aureus* isolates, though numbers were small in these subgroups.

#### Adverse effects

Retapamulin ointment was well tolerated in clinical trials. Irritation at the site of application was the commonest adverse event, with an incidence of 1 per cent.<sup>7</sup> It was associated with more adverse events at the application site than fusidic acid – nine out of 345 versus none out of 172.<sup>5</sup>

#### References

1. Clinical Knowledge Summaries. *Impetigo. Management issues*. March 2007. [www.cks.library.nhs.uk/impetigo/](http://www.cks.library.nhs.uk/impetigo/)

[in\\_depth/management\\_issues](#); accessed 22.2.08.

2. British Medical Association, Royal Pharmaceutical Society. *Anti-infective skin preparations*. Antibacterial preparations. *BNF 54*, September 2007.

3. GlaxoSmithKline. *First new topical antibiotic launched in UK for nearly a decade*. Press release. February 2008.

4. Oranje A, van der Wouden JC, Koning S, *et al*, on behalf of the 103469 Study Team. *Retapamulin ointment for the treatment of impetigo in adults and children: results of a phase III, placebo-controlled, double-blind trial (poster P16)*. 65th Annual Meeting of the American Academy of Dermatology, February 2007. [www.aad.org/meetings/previous/\\_doc/Posters\\_2007%20Annual%20Meeting.pdf](http://www.aad.org/meetings/previous/_doc/Posters_2007%20Annual%20Meeting.pdf); accessed 22.2.08.

5. Oranje AP, Chosidow O, Sacchidanand S, *et al*. Topical retapamulin ointment 1% versus sodium fusidate ointment 2% for impetigo: a randomized, observer-blinded non-inferiority study. *Dermatology* 2007; 215:331-40.

6. Free A, Roth E, Dalessandro M, *et al*. Retapamulin ointment twice daily for 5 days vs oral cephalexin twice daily for 10 days for empiric treatment of secondarily infected traumatic lesions of the skin. *Skinmed* 2006;5:224-32.

7. European Medicines Agency. *Altargo European Public Assessment Report*. February 2008. [www.emea.europa.eu/humandocs/PDFs/EPAR/altargo/H-757-en6.pdf](http://www.emea.europa.eu/humandocs/PDFs/EPAR/altargo/H-757-en6.pdf); accessed 22.2.08.

*By Steve Chaplin, a pharmacist who specialises in writing on therapeutics*

## Place in therapy

It is of interest that a new topical antibiotic has been launched for treatment of superficial skin infections likely due to *Staph. aureus* and/or *Strep. pyogenes*. For localised impetigo, topical antibiotic therapy is a reasonable choice. Fusidic acid and mupirocin are both effective agents. The *BNF* recommends the former as first choice; mupirocin should only be used to treat MRSA.

In recent years there has been an increasing incidence of staphylococci isolates with fusidic acid resistance. This may be because fusidic acid has been used in combination with topical steroids, often for prolonged and repeated periods in the treatment of atopic eczema. Fusidic acid resistance is of concern because it is used systemically, *eg* in osteomyelitis.

Retapamulin is a novel antibacterial, active against *Staph. aureus*

and *Strep. pyogenes*, and is only available for topical use. In a controlled trial retapamulin ointment twice daily appears to be as effective as fusidic acid three times daily in the treatment of impetigo in children and adults who had no more than 10 lesions and were not systemically unwell.<sup>1</sup> In this study retapamulin was successful in the relatively small number of cases in which the staphylococci were resistant to methicillin, fusidic acid and mupirocin. The trial was of 'non-inferiority' design, which has been criticised as being less useful than a superiority trial.<sup>2</sup>

Although *in-vitro* studies suggest that resistance to retapamulin only develops slowly, it will need exposure in clinical practice to know whether resistance will reduce the usefulness of this new agent sooner or later.

Retapamulin ointment is expensive (5g = £7.89) compared to fusidic acid (15g = £2.23) and mupirocin (15g = £4.38) and is

unlikely to be a first-line choice for topical treatment of impetigo, but it will have a place in treatment if the causative staphylococci are resistant to fusidic acid or there is a local microbiological policy of not using topical fusidic acid.

### References

1. Oranje AP, Chosidow O, Sacchidanand S, *et al.* Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: randomised, observer/blinded, noninferiority study. *Dermatology* 2007;215:331-40.
2. Snapinn SM. Noninferiority trials. *Curr Control Trials Cardiovasc Med* 2000;1:19-21.

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