Summary

Study Code Number
FUT 9404 INT

Study Title
Fucidin® versus fluoxacinil in skin and soft tissue infection.

Sub-title
A comparison of sodium fusidate tablets 250mg bd (Fucidin® tablets) and fluoxacinil capsules 250mg qid (Floxapen® capsules) in skin and soft tissue infection. A multicentre, prospective, randomised, double-blind, parallel-group study.

Objectives
To compare the overall clinical and bacteriological effect, symptomatic response, tolerability, acceptability and cost effectiveness of Fucidin® tablets with Floxapen® capsules in treating patients with skin and soft tissue infection. The primary criterion of response was the investigators' assessment of overall clinical treatment response ('cured' or 'improved') after five days of treatment.

Study design
The study was a multicentre, prospective, randomised, double-blind, parallel-group study. Eligible patients were randomly assigned to receive an initial five day course of Fucidin® tablets 250mg bd or Floxapen® capsules 250mg qid and were reviewed on day 6. Patients requiring a further five day course of antibiotic were seen again on day 11. A follow-up visit was conducted 14 days after completion of treatment for patients who were 'cured'. For patients receiving five days of treatment, assessments were therefore made at days 1 and 6, and if 'cured', at day 20 also. For patients receiving 10 days of treatment, assessments were therefore made at days 1, 6 and 11, and if 'cured', at day 25 also.
Duration of study phases
The study was divided into two phases: phase I, double-blind comparative treatment and phase II, follow-up. Phase I started at visit 1 (day 1) and ended at visit 2 (day 6) for patients who received five days of treatment or ended at visit 3 (day 11) for patients who received ten days' treatment. Phase II, follow-up, was only for patients rated as 'cured' at visit 2 or 3. Phase II started at the end of treatment (visit 2 or 3) and ended at the follow-up visit, 14 days later.

Total number of patients to be included in the study
The trial was designed to provide 240 analysable patients in each treatment group. To achieve this number, 530 patients were to be randomised.

Source of patients
All patients were entered by primary care physicians (General Practitioners) in the United Kingdom and Ireland.

Patient group studied
Patients of either sex, aged 18 years or more, with skin and/or soft tissue infection for which oral antibacterial therapy was indicated. Excluded were patients with cellulitis without a focal centre of infection, chronic/recurrent furunculosis, post-operative wound infection, leg ulcer, deep tissue abscess, hypersensitivity to study treatments, diabetes, immunosuppression, liver disease, or pre-existing infected dermatosis. Also excluded were those patients who were hospitalised or pregnant, or who had received antibacterial therapy in the last seven days.

Investigational products used
Patients were randomised to receive either Fucidin® tablets (sodium fusidate 250mg bd) or Floxapen® capsules (flucloxacillin 250mg qid) for five or 10 days, depending on response. Medication was supplied in blister packs, with each dose in an individual blister, and was to be taken orally with water, 30-60 minutes before meals.
Criteria for efficacy, safety, acceptability and cost effectiveness.

The primary efficacy criterion was the investigators' assessment of overall clinical treatment response ('cured' or 'improved') after five days treatment. This response was compared between the two treatment groups for all patients and also for the sub-group of patients in whom a pathogen (Staphylococcus aureus or β-haemolytic streptococci) was cultured at randomisation.

Secondary criteria of response included the investigators' assessment of overall clinical treatment response at end of treatment and at follow-up, changes in overall severity and signs/symptoms of the infection, bacteriological response, safety, acceptability of treatment to the patients, and cost-effectiveness.
Study procedures

The diagram below summarises study procedures.

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<thead>
<tr>
<th></th>
<th>Visit 1 (Day 1)</th>
<th>Visit 2 (Day 6)</th>
<th>Visit 3 (Day 11)</th>
<th>Follow-up Visit 3) (14 days after treatment complete)</th>
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<tbody>
<tr>
<td>Informed consent</td>
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<td>Inclusion/exclusion check list</td>
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<td>Other concurrent diagnoses</td>
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<td>Concurrent medication</td>
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<td>Clinical assessment of lesion</td>
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<td>Stratify to 'open'/ 'closed' lesion group</td>
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<td>Collecting of trial medication</td>
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</tbody>
</table>

1) Visit 3 was only required for those patients who had a second course of treatment.
2) Only required for those patients who had pathological material present.
3) Follow-up visit only required for patients rated 'cured' at end of treatment (visit 2 or visit 3).
4) Only dispensed to patients not rated 'cured' at visit 2 and for whom treatment was not discontinued due to inadequate response or adverse events.

Results

Four hundred and ninety-six patients were recruited, of whom 493 were randomised, 247 to Fucidin® and 246 to Floxapen®. Of the 247 patients randomised to Fucidin®, the mean age was 43 years, and there were 144 (58%) males and 103 (42%) females. Of the 246 patients randomised to Floxapen®, the mean age was 44 years, and there were 140 (57%) males and 106 (43%) females.
The safety population consisted of 489 patients (244 patients randomised to Fucidin®, 245 patients randomised to Floxapen®). The intention-to-treat population consisted of 476 patients (241 patients randomised to Fucidin®, 235 patients randomised to Floxapen®). The per-protocol population consisted of 465 patients (236 patients randomised to Fucidin®, 229 patients randomised to Floxapen®).

a) Efficacy results

For the primary efficacy criterion of investigators' assessment of overall clinical treatment response after five days treatment, both treatment groups achieved a high proportion of patients who were 'cured/improved'. This proportion was statistically significantly higher in the Floxapen® group than in the Fucidin® group, and this finding was consistent across all three populations studied (intention-to-treat population: 85% 'cured/improved' in the Fucidin® group, 92% 'cured/improved' in the Floxapen® group, p = 0.03; per-protocol population: 86% and 92% respectively, p = 0.03; bacteriologically evaluable population: 81% and 94% respectively, p = 0.01). For the sub-group of the bacteriologically evaluable population with Staphylococcus aureus sensitive to study treatment received, the proportions were also high in both treatment groups (85% 'cured/improved' in the Fucidin® group and 93% in the Floxapen® group).

At the end of treatment, the proportions of patients who were 'cured/improved' were also high (intention-to-treat population: 76% 'cured/improved' in the Fucidin® group, 81% 'cured/improved' in the Floxapen® group, p = 0.16; per-protocol population: 76% and 83% respectively, p = 0.06; bacteriologically evaluable population: 73% and 78% respectively, p = 0.43).

Relapse rates for 'cured' patients were low in the two treatment groups (per-protocol population: 6% in the Fucidin® group, 9% in the Floxapen® group).
The bacteriological success rate was high in both treatment groups at the end of treatment (88% in the Fucidin® group, 97% in the Floxapen® group), and statistically significantly higher in the Floxapen® group (p = 0.02). Patients' satisfaction with study treatment was also high in both treatment groups at the end of treatment. Eighty-two per cent in the Fucidin® group and 89% in the Floxapen® group found treatment 'very satisfactory' or 'satisfactory' (p = 0.04).

The cost of achieving an 'acceptable' treatment response was £11.14 in the Floxapen® group, and £15.02 in the Fucidin® group; for a 'good' treatment response £24.42 in the Floxapen® group and £29.15 in the Fucidin® group; and for an 'excellent' treatment response £30.73 in the Floxapen® group, and £38.12 in the Fucidin® group.

b) Safety Results
The safety profile was similar in the two treatment groups, with no statistically significant difference in the proportions of patients reporting adverse events (32% for Fucidin®, 31% for Floxapen®). More patients had adverse events in the gastro-intestinal System Organ Class than any other: 40 patients (16%) in each treatment group. Three patients in each treatment group had serious adverse events; in all cases these were considered to be of 'unlikely' relation to study medication.

Conclusions
Both Fucidin® and Floxapen® are effective in the treatment of patients with skin and soft tissue infections, and Floxapen® is statistically significantly more effective than Fucidin® with respect to the primary efficacy criterion (investigators' assessment of overall clinical treatment response after 5 days' treatment). The two treatments have a similar safety profile.