1. SUMMARY

TITLE
A prospectively randomized, cross-over study to evaluate the acceptability of Creon® granules in sachets with Creon® 8000 capsules in the treatment of pancreatic insufficiency in cystic fibrosis patients

INVESTIGATOR

STUDY DESIGN
This was an open, randomized, two-period, single-center, cross-over study in children with cystic fibrosis. The study consisted of two 6-week treatment periods. Patients were treated for pancreatic insufficiency with Creon® 8000 capsules and Creon® granules in sachets in randomized sequence.

It was planned that 40 patients entered the trial. However, this trial was stopped prematurely due to the low recruitment rate.

AIMS
Aim of the study was to evaluate the acceptability of Creon® granules in sachets in comparison to Creon® 8000 capsules in the treatment of pancreatic exocrine insufficiency due to cystic fibrosis.

METHODS
At study entry the parents answered a questionnaire concerning their child's general history of cystic fibrosis and Creon® therapy. At the end of each treatment period another questionnaire was answered concerning the treatment of the last 6 weeks. At the end of the study a preference for one or the other treatment was to be given.
DRUGS AND DOSAGES

Creon® was administered in two different forms:

- sachets of Creon® granules containing 750 mg pancreatin with an enzyme declaration of:
  
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Ph Eur. u.</th>
<th>USP u.</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipase</td>
<td>20 800</td>
<td>20 800</td>
</tr>
<tr>
<td>amylase</td>
<td>20 800</td>
<td>86 320</td>
</tr>
<tr>
<td>total proteases</td>
<td>1 200</td>
<td>75 000</td>
</tr>
</tbody>
</table>
  
- Creon® 8000 gelatin capsules containing 300 mg pancreatin with the following enzyme declaration:
  
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Ph Eur. u.</th>
<th>USP u.</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipase</td>
<td>8000</td>
<td>8000</td>
</tr>
<tr>
<td>amylase</td>
<td>9000</td>
<td>37 350</td>
</tr>
<tr>
<td>free proteases</td>
<td>210</td>
<td>13 125</td>
</tr>
</tbody>
</table>
  
The medication was to be taken orally at the time of food intake. The dosage was calculated by the investigator to give approximate parity concerning lipase dosage with the patient's usage of Creon® 8000 capsules.

Duration of treatment was 6 weeks with each formulation. Actually the mean duration was 44 days for sachets and 42 days for capsules, respectively. The average number of capsules taken was 29 (range of 10 to 52 capsules) and the average number of sachets taken was 12 (range of 4 to 22 sachets).

PATIENTS ENTERED

A total of 17 patients entered the study, 8 received the capsules first and 9 received the sachets first. All completed both 6-week treatment periods.

PATIENT CHARACTERISTICS

Eleven female and six male patients, with cystic fibrosis, aged between 0.4 and 12.1 years (mean of 4.2 years), entered the study. Mean duration of cystic fibrosis was 37 months (range of 1-83 months) and mean duration of Creon® therapy before entry into the study was 32 months (range of 1-74 months).

RESULTS

Ten parents of the 17 patients preferred the sachets and 5 the Creon® 8000 capsules, while 2 parents did not express a preference (p = 0.31, one-sided Binomial test concerning the hypothesis "p ≤ 0.5, where p = the probability for preferring Creon® granules in sachets").
However, with the assumptions stated in the protocol only a power of 0.5 could be reached with this low number of patients.

During treatment with Creon® 8000 capsules 7 patients (41%) experienced adverse events, while 9 patients (53%) had adverse events during treatment with Creon® sachets. Infection (4 patients), increased cough (3 patients), ear infection, fever, and pharyngitis (reported by 2 patients each) were the adverse events which occurred in more than one patient. No patient was withdrawn from the study due to adverse events or experienced serious adverse events.

CONCLUSION

- Although the expected trend towards patients preference in favour of Creon® sachets was confirmed, the small number of 17 patients does not allow any conclusion.

- Safety was good for Creon® granules in sachets as well as for Creon® 8000 capsules.