SYNOPSIS

INN : ROXITHROMYCIN

Study number : FF/94/965/64

Study title : Evaluation of the efficacy and tolerance of roxithromycin 5-8 mg/kg/day taken twice daily and clarithromycin 11-21 mg/kg/day taken twice daily in a 5 to 10 days treatment of lower respiratory tract infections in children.

CSR date : February 2001

The study results and synopsis are supplied for informational purposes only.

Not all of the study results have necessarily been reviewed by the Regulatory Authorities.

The decision to prescribe and take a product should always be made on the basis of the most recent version of the product information and product package insert in the country of prescription.

PDF name: Roxithromycin – Study 2
### SYNOPSIS

<table>
<thead>
<tr>
<th>Name of company :</th>
<th>Individual study table referring to part of the dossier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoechst Marion Roussel / Aventis Pharma</td>
<td>Volume:</td>
</tr>
<tr>
<td>Name of finished product :</td>
<td>Page:</td>
</tr>
<tr>
<td>Rulide, Rulid</td>
<td></td>
</tr>
<tr>
<td>Name of active ingredients(s) :</td>
<td>(For National Authority use only)</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td></td>
</tr>
</tbody>
</table>

**Report type**
Abbreviated clinical study report, final draft

**Report origin**
Aventis Pharma B.V. previously Hoechst Roussel B.V. respectively Hoechst Marion Roussel, Hoevelaken, The Netherlands

**Title of the study**
Evaluation of the efficacy and tolerance of roxithromycin 5-8 mg/kg/day taken twice daily and clarithromycin 11-21 mg/kg/day taken twice daily in a 5 to 10 days treatment of lower respiratory tract infections in children.

**Investigator**
Individuals are listed in the list of investigators

**Study centre(s)**
Twenty-three (23) active centres in Argentina, Belgium, Brazil, Peru, The Netherlands and South Africa (See list of investigators). Thirteen centres were non-active after initiation. One Peruvian centre was excluded from the analysis after a Central Quality Assurance audit was performed. During the second inclusion period, only 6 centres were active (centres from Argentina, Belgium, Brazil and The Netherlands).

**Publication (reference)**
-

**Study period (years)**
2 years, from 04/96 to 07/97 and from 11/97 to 03/98

**Clinical Phase:** IIIb

**Objectives**
The primary objective was to compare the efficacy of roxithromycin 5-8 mg/kg/day taken twice daily and clarithromycin 11-21 mg/kg/day taken twice daily in a 5 to 10 days treatment of lower respiratory tract infections in children. The secondary objectives were to compare between the two treatment options:

- Tolerance
- Acceptability and compliance
- Cost-effectiveness.

**Methodology**
International, multicentre, open, comparative, centrally randomised parallel group study.

**Number of subjects**
In total 351 patients were randomised during the first inclusion period. Thirty patients from one Peruvian centre and one randomised patient who did not start treatment were excluded from analysis. Together with the protocol violations, the target of 310 evaluable patients was not reached. Therefore a second inclusion period was started resulting in 359 patients randomised of which 9 patients were excluded to result in 350 patients for the ITT- analysis. For the PP-analysis another 19 patients were excluded to result in 331 patients.

**Diagnosis and criteria for inclusion**
Children with a weight of 8 up to 20 kg (age ≥ 3 months) of either sex, outpatients, with a diagnosis of lower respiratory tract infection (LRTI) presumed to be of bacterial origin.
Test product, dose & mode of administration, batch numbers
Roxithromycin (RU28965) 5-8 mg/kg/day B.I.D, taken as a tablet for oral suspension.
Batch numbers: CC26126-157 and L22

Duration of treatment
Acute Bronchitis: min. 5 days / max. 10 days
(Broncho-) pneumonia: 10 days.

Reference therapy, dose & mode of administration, batch numbers
Clarithromycin 11-21 mg/kg/day twice daily, taken as an oral suspension (commercially available).
Batch numbers: 12020VA95L20 and 32284VA97H29

Criteria for evaluation
Clinical efficacy:
General physical examination, infection-related signs and symptoms during each visit.

Bacteriological efficacy:
Whenever possible appropriate cultures were performed at each visit

Safety:
General signs, adverse events.

Interim analysis
No interim analysis was performed

Statistical methods
The intention-to-treat (ITT) analysis was performed for all variables.
The ITT analysis was carried out for all patients with both a pre-treatment and a during treatment and/or post-treatment value.
A per-protocol (PP) analysis was only performed for the primary efficacy variable, being the clinical efficacy. Included were all patients with both a pre-treatment value and with follow-up data, but excluding major protocol violators.
Data were summarised in terms of means and standard deviations, or in terms of frequencies, as appropriate.
Statistical tests were carried out at a 5% level of significance ($\alpha$). All tests were two-sided, with the exception of Blackwelder’s test, which was used to compare the overall clinical success rates.

Results – Study subjects and conduct
Demographic characteristics at inclusion
In total 359 patients were included in the analysis of this study. Two-hundred-and-twenty patients (61.3%) were diagnosed with an acute bronchitis (49.5% ROX, 50.5% CLA), forty-nine (13.6%) had a lobar-pneumonia (55.1% ROX, 44.9% CLA), eighty-nine (24.8%) had a bronchopneumonia (44.9% ROX, 55.1% CLA). No statistical significant differences were seen between the two treatment groups with respect to demographics and medical history.

Thirty patients did not complete the study (17 lost to follow-up, 6 discontinuation for adverse events, 5 discontinuation for lack of efficacy, 2 discontinuation due to consent related issues).

For 16 patients, 8 in each treatment group, the final diagnosis differed from the initial diagnosis.

Deviations in the intake of the treatment were observed in 30 patients (5 cases were considered as a major protocol violation)

Hundred thirty two (132) protocol violations were identified in 98 patients. (Hundred eighteen times one of the visits was outside the time window, 5 patients received forbidden medication, 2 patients had a prolonged treatment, 2 consent related protocol violations, 1 treatment deviation, 1 bad compliance, 1 randomisation error, 1 missing visit, 1 weight < 8 kg). For the PP-protocol analysis 331 patients were included.
Results – Efficacy
Clinical results were evaluated according to the criteria described above.
The overall clinical success rate at the end of treatment was 94.6% for ROX and 96.2% for CLA (PP-analysis).

<table>
<thead>
<tr>
<th>Clinical results visit 3 – End of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-analysis</td>
</tr>
<tr>
<td>ROX</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Overall success rate</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Success</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Acute Bronchitis</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Success</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Success</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Lobar-pneumonia</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Success</td>
</tr>
<tr>
<td>Failure</td>
</tr>
</tbody>
</table>

Results – Safety
A total of 73 events in 52 ROX patients and 76 events in 58 CLA patients were reported. Most frequently occurring complaints were related to the digestive and respiratory system. For about 66% of the adverse events, the intensity was mild, 30% was moderate and only 4% was rated as severe.
The number of drug-related adverse events was respectively 24 in 21 (12.4% ROX) patients and 23 in 18 (9.9% CLA) patients.
In total 10 serious adverse events were reported, 8 in the ROX group and 2 in the CLA group. No event was considered to be related to any of the study drugs.

Conclusions:
The overall clinical response at visit 3 (end of treatment) in ROX and CLA was satisfactory: 94.6% for ROX and 96.2% for CLA in the PP-analysis. We may conclude from this study that ROX was as effective as CLA.
The number of drug-related adverse events was almost equal and low in both groups: 24 (in 21 ROX patients) and 23 (in 18 CLA patients) respectively.
In summary we may conclude from this study that both drugs appeared to be effective and well tolerated in the treatment of children with lower respiratory tract infections.