Establishment of Quality Control Ranges for Testing the Susceptibility of Target Organisms to Solithromycin (CEM-101) by Disk Diffusion

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Abstract

Background: Solithromycin is a novel fluoroketolide undergoing Phase 2 trials for the treatment of community-acquired pneumonia. With any new agent, it is important to have available reliable and reproducible methods of evaluating in vitro activity during development and post-approval. Solithromycin disk zone sizes correlate well with broth microdilution MICs demonstrating the feasibility of disk diffusion testing of solithromycin. This study establishes quality control ranges to be used for disk diffusion susceptibility testing of solithromycin during development and post-approval.

Methods: Quality control ranges for the disk diffusion testing of solithromycin (15 micrograms) were determined per CLSI guidelines (M23-A3). 9 separate laboratories each tested 10 independent replicates of each evaluated ATCC QC organism (Staphylococcus aureus ATCC 29213, Staphylococcus pneumoniae ATCC 49619, and Haemophilus influenzae ATCC 49247) across three lots of media from different manufacturers against two disk lots of solithromycin (one from MAST and one from BD). The data generated for the zone diameters were analyzed using central tendency statistical analysis by both Gavin Statistic and Rangefinder to determine the CLSI approved QC ranges. Data for the zone diameter was also analyzed to determine the mean and mode zone diameter for each organism. In accordance with CLSI M23, reliable QC ranges have been established for disk diffusion testing of solithromycin against target respiratory pathogens. These ranges will be used going forward to monitor disk test results going during the clinical development of solithromycin and beyond.

Results: The results for S. aureus 25923 and S. pneumoniae 49619 were within the approved 25-33 mm zone range. For all evaluated organisms, there was little variation across media lots and disk lots (Table 5).

Conclusions: The proposed ranges are suitable for quality control testing of solithromycin and the overall performance was shown in the Table 1. These ranges take into account intra-laboratory, intra-media lot, and intra-disk lot variation.

Methods: Methods

- Solithromycin is an investigational fluoroketolide that is more potent than existing macrolides, and has an extended spectrum of antimicrobial activity.
- Active against key bacterial pathogens associated with community-acquired bacterial pneumonia (CABP).
- Generally 8-16 fold more active than azithromycin and 2-4 more active than solithromycin in vitro.
- Active against mycobacteria, malaria parasites, and bioterrorism organisms.
- Currently in Phase 2 clinical trials for CABP.

Introduction

- The study was done according to the criteria as defined in CLSI M23-A3. Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters.
- Each of nine laboratories participated.
- Each site tested three different agar lots.
- Testing was performed for solithromycin generating zone diameter values in millimeters (mm) for two disk lots on three different media lots for each of ten replicates (3 x 3 x 10 = 90 results) at nine sites yielding 945 zone diameters for each organism tested.

TABLE 1.  CLSI approved QC ranges for the disk diffusion testing of Solithromycin.

<table>
<thead>
<tr>
<th>Organism</th>
<th>QC range (mm)</th>
<th># mm</th>
<th>Results (n)</th>
<th>% of results in range</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus ATCC 29213</td>
<td>20-36</td>
<td>180</td>
<td>540</td>
<td>100</td>
</tr>
<tr>
<td>S. pneumoniae ATCC 49619</td>
<td>12-24</td>
<td>180</td>
<td>540</td>
<td>100</td>
</tr>
<tr>
<td>H. influenzae ATCC 49247</td>
<td>16-30</td>
<td>180</td>
<td>540</td>
<td>100</td>
</tr>
</tbody>
</table>

TABLE 2. Central tendency statistical analysis of data by Gavin Statistic and Rangefinder

<table>
<thead>
<tr>
<th>Organism</th>
<th>Gavin statistic</th>
<th>Rangefinder</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus ATCC 29213</td>
<td>22-30</td>
<td>20-36</td>
</tr>
<tr>
<td>S. pneumoniae ATCC 49619</td>
<td>25-33</td>
<td>20-36</td>
</tr>
<tr>
<td>H. influenzae ATCC 49247</td>
<td>22-30</td>
<td>20-36</td>
</tr>
</tbody>
</table>

Conclusion: In accordance with CLSI M23, reliable QC ranges have been established for disk diffusion testing of solithromycin against target respiratory pathogens.

Acknowledgements

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