Solithromycin is a new chemical entity under development by Cempra Pharmaceuticals as a fourth-generation macrolide antibiotic and first fluoromacrolide. The chemical structure of solithromycin is shown in Figure 1 below.

![Chemical structure of solithromycin](Figure 1)

Solithromycin is currently completing Phase 3 of clinical development for the treatment of community-acquired bacterial pneumonia in adult patients. As part of Cempra’s Pediatric Investigation Plan, it was necessary to initiate development activities for a pediatric dosage form for the same indication. A powder for oral suspension dosage form was selected for development because it can promote better patient compliance than liquid formulations and is well suited for the pediatric developmental stages [1]. All macrolides, including clarithromycin, have bitter taste that must be masked for use in pediatric oral suspensions [2, 3]. Solithromycin was found to be less bitter than clarithromycin in an initial taste evaluation. Therefore solithromycin oral suspension taste masking was included in formulation development.

**Approach:**

The development of a taste masked solithromycin powder for oral suspension was conducted by Senopsys LLC (Woburn, MA) following the sensory-directed approach to taste optimization illustrated in Figure 2.

![Taste Optimization Approach](Figure 2)

**Methods Continued:**

Panelists used the following procedure to evaluate suspension samples:

1. The panelists cleansed their palates with spring water and unsalted crackers.
2. 5mL of sample was dispensed into individual 1-ounce plastic cups using a graduated oral syringe and distributed to each panelist.
3. Swishing the contents around the oral cavity for 10 seconds and expectorated. During this step, the saliva produced by the panelists was captured in the cups.
4. The panelists then independently evaluated and recorded the aftertaste characteristics at periodic intervals out to 30 minutes after flavor presentation.
5. The panelists noted their individual results and a preliminary Flavor Profile was generated for the sample.
6. Steps 1 through 4 were repeated for a second evaluation of the sample using the preliminary Flavor Profile from Step 3 as a guide, with the panelists noting any necessary modifications.
7. The panelists noted their individual results and a final Flavor Profile was developed for the sample.

The Flavor Leadership Criteria (5) were used to interpret sensory results and guide the development of products that can be differentiated on the basis of perceived flavor quality.

1. **Aromatic identity:** immediate impact of the identifying flavor, e.g., orange, berry, mint
2. **Amplitude:** rapid development of balanced, full flavor
3. **Synchronous:** flavors that are compatible with the flavor system, e.g., cooling (mint, e.g., menthol)
4. **Offnotes:** minimal aversive attributes, e.g., bitterness, tingling/irritation, astringency
5. **Sustained:** sufficient duration of sweetness and favoring aromatics to cover aversive attributes

The initial taste assessment of an unflavored suspension of solithromycin in phosphate buffer pH 6.4 was used to guide the formulation development, as shown Table 1 below.

![Flavor Profile Definitions](Figure 3)

**Flavor Profile Definitions**

<table>
<thead>
<tr>
<th>Flavor Profile Definitions</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amplitude:</strong></td>
<td>initial intensity of the balance and fullness of a flavored product</td>
</tr>
<tr>
<td><strong>Aromatic identity:</strong></td>
<td>immediacy of the identifying flavor, e.g., orange, berry, mint</td>
</tr>
<tr>
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<tr>
<td><strong>Sustained:</strong></td>
<td>sufficient duration of sweetness and favoring aromatics to cover aversive attributes</td>
</tr>
</tbody>
</table>

Character Notes: Aromatic, basic tastes, and feeling factors (status in order of appearance along with a characteristic taste and intensity)

**Method Continued:**

Throughout the study, the flavor of the sample was measured using the Flavor Profile method of descriptive sensory analysis (5), which uses trained pharmaceutical sensory assessors to rank and rate a sample on a numerical scale.

**Methods Continued:**

To the complete the formulation, various identifying flavors were evaluated. Two flavors (cherry and bubblegum) were selected, generating the final two taste-masked formulations shown in Table 4. These compositions were then transferred to a Contract Development and Manufacturing site for scale-up and process development studies. The final two taste-masked formulations has been selected and the manufacture of clinical supplies for pivotal studies is ongoing.

![Sucrose/Aspartame/Magnasweet Bitterness Profile](Figure 6)

**Figure 6: Sucrose/Aspartame/Magnasweet Bitterness Profile**

As the mimic system represents an approximation of the drug product, the Bitrex mimic was replaced with 300mg solithromycin and evaluated by the sensory panelists to verify if the white base formulation performs as expected. Using the results of this confirmation round, the sweeter system was further refined (reducing sucrose and increasing aspartame), and a lead aspartame concentration (1%) was selected for advancement as shown in Figure 7.

![Sucrose/Aspartame Bitterness Profiles](Figure 4)

**Figure 4: Desensitizes Bitterness Profiles**

Based on the lingering bitterness profile, it was clear that high intensity sweeteners would be needed. Several options were evaluated in the study on a bitter masking system and sodium saccharin, aspartame, sorbitol, and sucrose. Ultimately, sucrose and aspartame is the leading high intensity sweeter candidate due to its beneficial bitter masking and chemical compatibility with the solithromycin-functional base.

![Sucrose/Aspartame Bitterness Profiles](Figure 5)

**Figure 5: Sucrose/Aspartame Bitterness Profiles**

As part of Cempra’s Pediatric Investigation Plan, solithromycin is currently completing Phase 3 of clinical development for the treatment of community-acquired bacterial pneumonia in adult patients. As part of Cempra’s Pediatric Investigation Plan, it was necessary to initiate development activities for a pediatric dosage form for the same indication. A powder for oral suspension dosage form was selected for development because it can promote better patient compliance than liquid formulations and is well suited for the pediatric developmental stages. As the principal taste masking challenge was a lingering bitterness, caffeine, sucrose octaacetate and denatonium benzoate (Bitrex®) were evaluated to serve as a mimetic for solithromycin. Based on the results, Bitrex at a concentration of 1.5% PPM was selected as a suitable mimetic. The bitterness profile of various concentrations of Bitrex is shown in Figure 4 below.

![Sucrose/Aspartame Bitterness Profiles](Figure 3)

**Figure 3: Sucrose/Aspartame Bitterness Profiles**

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![Sucrose/Aspartame Bitterness Profiles](Figure 2)

**Figure 2: Sucrose/Aspartame Bitterness Profiles**

As the mimic system represents an approximation of the drug product, the Bitrex mimic was replaced with 300mg solithromycin and evaluated by the sensory panelists to verify if the white base formulation performs as expected. Using the results of this confirmation round, the sweeter system was further refined (reducing sucrose and increasing aspartame), and a lead aspartame concentration (1%) was selected for advancement as shown in Figure 7.

![Sucrose/Aspartame Bitterness Profiles](Figure 1)

**Figure 1: Sucrose/Aspartame Bitterness Profiles**

As part of Cempra’s Pediatric Investigation Plan, solithromycin is currently completing Phase 3 of clinical development for the treatment of community-acquired bacterial pneumonia in adult patients. As part of Cempra’s Pediatric Investigation Plan, it was necessary to initiate development activities for a pediatric dosage form for the same indication. A powder for oral suspension dosage form was selected for development because it can promote better patient compliance than liquid formulations and is well suited for the pediatric developmental stages. As the principal taste masking challenge was a lingering bitterness, caffeine, sucrose octaacetate and denatonium benzoate (Bitrex®) were evaluated to serve as a mimetic for solithromycin. Based on the results, Bitrex at a concentration of 1.5% PPM was selected as a suitable mimetic. The bitterness profile of various concentrations of Bitrex is shown in Figure 4 below.

![Sucrose/Aspartame Bitterness Profiles](Figure 7)

**Figure 7: Bitterness Profiles of Leading Aspartame-Sweetened Solithromycin Formulations**

**Conclusions**

Taste masked formulations are used to improve pediatric compliance of bitter drug, such as macrolide antibiotics. A Flavor Profile Method of descriptive sensory analysis was used to select a palatable suspension formulation for solithromycin to be used in Phase 1 pediatric studies. The formulations has since been further refined for pivotal clinical studies. The Flavor Profile Method of descriptive sensory analysis is a useful tool to guide the development of formulations suitable for pediatric patients.

**References**

[4] Prabhavathi Fernandes, Melissa Allaband, Jeffrey Worthington, NV-10,506, NV-20,629, Magnasweet 100, Sucrose NF, Tribasic Anhydrous, Simethicone, Aerosil 200, Monoammonium glycyrrhizinate (Magnasweet™) can extend and support sweetness in the absence of some formtions and was evaluated in the leading aspartame-sweetened mimetic system (Figure 6).
[5] NV-10,506
[6] NV-20,629