The Federal Regulation of New Drugs

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Pleconaril

First antiviral drug with activity against picornaviruses, the predominant cause of the common cold.
Indication

Pleconaril is indicated for the treatment of acute picornaviral upper respiratory illness (the common cold) in adults.
Current Management of Viral Respiratory Illness

- Influenza virus
  - 4 marketed antiviral drugs
  - Vaccines

- Respiratory syncytial virus
  - Prophylactic antibody products
  - Aerosolized ribavirin

- Picornavirus
  - No marketed antiviral drugs
  - No prospect for vaccine
  - Current treatments inadequate
Human Picornaviruses

Rhinoviruses
Common Cold
Otitis Media
Sinusitis
Exacerbation of Asthma, COPD, and CF
LRT Infections in Immunocompromised

Enteroviruses
Common Cold
Herpangina
Hand-foot-and-mouth
Meningitis/encephalitis
Myocarditis
Neonatal Sepsis
Meningoencephalitis
Incidence of Colds

- Annual incidence (colds per year)
  - Children: 6 to 8
  - Adults (16 to 45): 2 to 3
  - Adults (>45 years): 1

- Rhinovirus infections
  - 50% of colds on annual basis with peaks in spring and fall (up to 80%)

Dingle, et al. The Press of Western Reserve University. 1964;1
Natural History of Picornavirus Colds in Adults

- 69% self-diagnosed cold within 8 hours
- Sore throat most common first symptom
- Rhinorrhea most bothersome symptom
- Fever uncommon
- Sleep disturbed 4 days
- 7-to 11-day duration of symptoms
  - 25% have symptoms for 2 weeks

Picornavirus Colds Pathogenesis

Virus Infection of Nasal Epithelium

- Proinflammatory Cytokines (IL-1, -6, -8)
- Secondary Inflammation (PMNs, kinins)
- Neurogenic Responses
- Tracheobronchial Infection
- Cholinergic Stimulation
- Vasodilation
- Serum Transudation
- Mucus Secretion
- Airway Hyperreactivity

- Sore Throat
- Sneezing
- Nasal Obstruction
- Rhinorrhea
- Cough
Current Management of Colds

- 75% of patients with colds self medicate
- Symptom relief treatments
  - Cough preparations (84%), combination cold products (83%), analgesics (83%), decongestants (57%), antihistamines (56%)
  - Benefits are variable and transient
  - Do not shorten illness duration
  - Side effects and precautions

SVI Consumer Segmentation, October 2001
Current Management of Colds

• Leading reason for physician visits
  • ~15% of colds result in an office visit

• Antibiotics
  • 30-50% of visits result in antibiotic prescription
  • No reduction in symptoms or complications

• No treatment for the underlying viral cause

Gonzales, et al. JAMA. 1997;278:901
Pleconaril Mechanism of Action

Blocks uncoating and attachment by binding into a hydrophobic pocket within the capsid
Human Pharmacokinetic Profile

400 mg Single Dose (Commercial Tablet)

Conc. (µg/mL)

Time (h)

$\text{MIC}_{90}$

$\text{MIC}_{76}$

$t_{1/2_a} = 2.8 \text{ h}$

$t_{1/2} \approx 180 \text{ h}$
Human Metabolism

Pleconaril

CH$_3$ Oxidation = N-OH
Isoxazole Ring Opening = N-O-Glucuronidation
Effects of Pleconaril on CYP 450

- Inhibition
  - *In vitro*
    - No inhibition of CYP 2A6, 2C8, 2D6, 2E1, 3A4
    - Weak inhibition of CYP 1A2, 2C9, 2C19
  - Phase I
    - No effect on S- or R-warfarin (2C9 probe)
    - Small effects on theophylline (1A2 probe) AUC and $t_{1/2}$

- Induction of CYP 3A
  - Phase I
    - Increased CYP 3A activity with midazolam and ethinylestradiol
Oral Contraceptive Interaction Study

No clinically significant change in $C_{\text{max}}$
34% decrease in ethinylestradiol AUC
No effect on norethindrone pharmacokinetics
Preclinical Safety

- Low acute toxicity potential
- No significant findings in 1- and 6-month studies
- No genotoxicity
- No teratogenicity
- No effects on male or female fertility
- No effects on growth, viability, development, or reproductive performance of offspring following maternal exposure *in utero* through weaning
Clinical Development of Pleconaril for the Common Cold

- Phase II Coxsackievirus A21 challenge study
- Two pivotal Phase III studies

- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002

- Three Phase II studies in natural colds
- Two Phase II pediatric studies
- One 6-week adult prophylaxis study
Pivotal Phase III Clinical Trials

- Two randomized, placebo-controlled trials of identical design
- 2096 patients randomized
  - Protocol 043: 1052 patients
  - Protocol 044: 1044 patients
- 197 centers across the US and Canada
- Enrollment from August – November 2000
Entry Criteria

- Otherwise healthy subjects = 18 years old
- Answer ‘Yes’ to “Do you have a cold today?”
- Moderate or severe rhinorrhea
- At least one other respiratory symptom
  - nasal congestion, cough, sore throat
- Symptom duration = 24 hrs
- Exclusions
  - active allergic rhinitis or asthma
  - fever = 100°F
Primary Efficacy Endpoint

- Time from initiation of study drug to
  - Absence of rhinorrhea
  - Five other cold symptoms absent or mild
  - Sustained for four consecutive reporting periods (~48 hrs)
  - Without use of concomitant cold symptom relief medications
- Endpoint occurs at the beginning of the 48-hour interval
### Primary Efficacy Endpoint: ITT-I

<table>
<thead>
<tr>
<th>Days</th>
<th>Study 043</th>
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<th>Study 044</th>
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<tbody>
<tr>
<td></td>
<td>Placebo N=328</td>
<td>Pleconaril N=337</td>
<td>p-value</td>
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<td>25&lt;sup&gt;th&lt;/sup&gt; Percentile</td>
<td>4.1</td>
<td>3.3</td>
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<td>3.3</td>
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<tr>
<td>Median</td>
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<td>6.6</td>
<td>0.037</td>
<td>7.7</td>
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<tr>
<td>75&lt;sup&gt;th&lt;/sup&gt; Percentile</td>
<td>11.7</td>
<td>10.8</td>
<td>12.3</td>
<td>10.4</td>
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</table>
Primary Efficacy Endpoint
Studies 043 and 044

Study 043

Study Day

Percentage of Patients Reaching Endpoint

Placebo

Pleconaril

Study 044

Study Day

Placebo

Pleconaril
## Primary Endpoint: ITT and RT-PCR Negative

<table>
<thead>
<tr>
<th></th>
<th>Study 043</th>
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<td>Placebo</td>
<td>Pleconaril</td>
<td>Placebo</td>
<td>Pleconaril</td>
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<tr>
<td>ITT</td>
<td>N=526</td>
<td>N=526</td>
<td>N=524</td>
<td>N=520</td>
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<tr>
<td>Median Days</td>
<td>6.9</td>
<td>6.4</td>
<td>7.1</td>
<td>6.2</td>
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<tr>
<td>p-value</td>
<td>0.201</td>
<td></td>
<td>0.015</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Study 043</th>
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<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Pleconaril</td>
<td>Placebo</td>
<td>Pleconaril</td>
</tr>
<tr>
<td>RT-PCR Negative</td>
<td>N=200</td>
<td>N=189</td>
<td>N=168</td>
<td>N=176</td>
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<tr>
<td>Median Days</td>
<td>5.9</td>
<td>6.1</td>
<td>5.9</td>
<td>6.0</td>
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<tr>
<td>p-value</td>
<td>0.639</td>
<td></td>
<td>0.776</td>
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</table>
Clinical Safety
Exposure to Pleconaril

Total (5 to 7 days)

- Adults: 3218
- Children: 678

- Phase 2/3: 2868
- Phase 1: 350

- Cold: 2472
- Meningitis: 396

Cold Tablet: 1480

Prophylaxis (6 weeks)

- 712
### Adverse Events (≤ 5%)

**Adult Phase 2/3 Cold Studies (Tablet)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1484</th>
<th>Pleconaril 400 mg TID N=1480</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>6 (0.4%)</td>
<td>7 (0.5%)</td>
</tr>
<tr>
<td>=1 AE</td>
<td>799 (54%)</td>
<td>809 (55%)</td>
</tr>
<tr>
<td>Headache</td>
<td>323 (22%)</td>
<td>348 (24%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>97 (7%)</td>
<td>114 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (4%)</td>
<td>89 (6%)</td>
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</tbody>
</table>
### Discontinuations Due to Adverse Events (≤ 0.3%)

#### Adult Phase 2/3 Cold Studies (Tablet)

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1484</th>
<th>Pleconaril 400 mg TID N=1480</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to AE</td>
<td>40 (2.7%)</td>
<td>51 (3.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (0.4%)</td>
<td>7 (0.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (0.2%)</td>
<td>9 (0.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (0.3%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (0.3%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5 (0.3%)</td>
<td>4 (0.3%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (0.1%)</td>
<td>4 (0.3%)</td>
</tr>
</tbody>
</table>
Clinical Laboratory Safety

No clinically significant changes in
- Hematology values
- Renal or liver function values
- Laboratory safety values
# Menstrual Disorders: Six-Week Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>400 mg QD</th>
<th>400 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Women</strong></td>
<td>51/245</td>
<td>79/245</td>
<td>66/232</td>
</tr>
<tr>
<td></td>
<td>(21%)</td>
<td>(32%)</td>
<td>(28%)</td>
</tr>
<tr>
<td><strong>OC Users</strong></td>
<td>20/81</td>
<td>52/98</td>
<td>40/58</td>
</tr>
<tr>
<td></td>
<td>(25%)</td>
<td>(53%)</td>
<td>(69%)</td>
</tr>
</tbody>
</table>
Menstrual Disorders: Summary

- No event was severe in pleconaril groups
- <1% in each group discontinued treatment
- 3.5% of women taking OCs and pleconaril in 5-7 day cold treatment studies reported a menstrual disorder
- Mechanism: Likely the result of increased CYP 3A4 activity
## Pregnancy: Six Week Study

<table>
<thead>
<tr>
<th>Age</th>
<th>BC Method</th>
<th>Estimated Conception</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=245 women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Condom</td>
<td>Wk 9</td>
<td>Spont. abortion</td>
</tr>
<tr>
<td>Pleconaril 400 mg QD (N=245 women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Condom</td>
<td>– 1.7 wk</td>
<td>Spont. abortion</td>
</tr>
<tr>
<td>Pleconaril 400 mg BID (N=232 women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Abstinence</td>
<td>Wk 1.7</td>
<td>Ongoing</td>
</tr>
<tr>
<td>29</td>
<td>OC</td>
<td>Wk 1.4</td>
<td>Elect. abortion</td>
</tr>
<tr>
<td>34</td>
<td>Condom</td>
<td>Wk 3.6</td>
<td>Ongoing</td>
</tr>
<tr>
<td>31</td>
<td>OC</td>
<td>Wk 6</td>
<td>Ongoing</td>
</tr>
<tr>
<td>30</td>
<td>Abstinence</td>
<td>Wk 3.3</td>
<td>Elect. abortion</td>
</tr>
</tbody>
</table>
Risks: Drug Interactions

- Theophylline
  - Slight increase in steady-state plasma concentrations

- Oral contraceptives
  - Increased incidence of menstrual irregularities

- CYP 3A substrates
  - Decreased plasma concentrations of drugs with narrow concentration response relationships
Guidance for Physicians

- Empiric treatment
  - Self-diagnosed cold with rhinorrhea and no fever
  - Start pleconaril within a day of onset of cold symptoms

- Information for patients
  - Take pleconaril with food (meal or snack)
  - Most common side effects: headache, nausea, diarrhea
  - Women on OCs: use an additional method of birth control

- Drug interactions: refer to labeling

- Limited data in elderly and patients with co-morbidities
Questions to the Advisory Committee

- Discuss the efficacy of pleconaril for treatment of acute VRI in adults
  - The efficacy results from studies 843-043 and 843-044
  - The manner in which pleconaril will likely be used in clinical practice
  - Prescribed to symptomatic patients with no rapid diagnostic test available to identify infected patients
  - The need to institute pleconaril within 24 hours of onset of the first symptoms
Questions to the Advisory Committee

• Discuss the safety of pleconaril in adult patients with symptoms of acute VRI
  - Pleconaril’s effect on cytochrome CYP3A4
  - The frequency of menstrual disorders occurring in females using OCs while being treated with pleconaril and potential risk for unintended pregnancy
  - The apparent pharmacodynamic interaction with theophylline
Questions to the Advisory Committee

- Does the safety and efficacy profile of pleconaril support its approval for treatment of VRI in adults?