Zyprexa Global Issues

Opportunity/Issues/Competition

October 14, 15, 1998
Competitive Update

Focus on Risperdal & Zotepine Profile

October 14-15, 1998
Janssen, US Promotional Mix

- Janssen Sales Performance

Message

CME

Sales force

Promotional $
Janssen '97 US sales

- Duragesic $138 m
- Sporanox $140 m
- Nizoral $146
- Hismanal $98 m
- Propulsid $397 m
- Risperdal $555 m

October 14-15, 1998
# Janssen Product Portfolio

## US Sales

<table>
<thead>
<tr>
<th>Product</th>
<th>Class</th>
<th>'97 Sales</th>
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<tbody>
<tr>
<td>Risperdal</td>
<td>anti-psychotic</td>
<td>$555M</td>
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<tr>
<td>Propulsid</td>
<td>anti-ulcer</td>
<td>$397 M</td>
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<tr>
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<td>anti-fungal</td>
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<td>antihistamine</td>
<td>$98 M</td>
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</tbody>
</table>

*October 14-15, 1998*
Janssen US Risperdal Message

- "Rethink Risperdal"
  - Schizophrenia, Bipolar, Elderly psychosis

- Positive and negative symptoms + safety profile and cognitive function benefits that help redefine efficacy
  - Impaired cognition can affect...
  - Impaired cognition may be associated with...
  - Low risk of anticholenergic side effects and their impact on cognitive function...Zyprexa...

- Weight gain - lack of it may encourage compliance
- Cost - 2, 4, 6mg Vs. 10, 15, and 20mg Zyprexa

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Janssen US Risperdal Message

- Person to Person - patient compliance & support
- Dosing flexibility (initial dosing for acute to chronic patients - 1mg BID, titrate at daily to weekly intervals, now approved in QD dosing)
- Benefits for the elderly
  - Low EPS
  - sedation
- Receptor profiles
  - Zyprexa high M₁, H₁, and α₁ affinity

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Risperdal Vs. Zyprexa
Promotional Spend

October 14-15, 1998

source: IMS
Janssen CME program - 4/25/98

- Efficacy of 6mg Risperdal superior to 20mg Haldol for + and - sx's
- Efficacy of 15mg Zyprexa superior to Haldol for - sx's, *not superior* on + sx's
- Co-prescription of typicals:
  - Zyprexa, 22% of pts  Risperdal, 6%
  - *Data from "US psychs"*
- Average dose for schizophrenia:
  - Zyprexa, 15.7mg  Risperdal, 4.1mg

Risperdal superior for both + and - sx's, Zyprexa only for -, which may explain higher rate of adjunctive typical use

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Janssen CME Program

- Treatment Resistant Schizophrenia:
  - Risperdal 6mg equal to Clozaril (150-400mg)
  - No difference in EPS
  - Zyprexa 25mg not superior to Thorazine
    - Less EPS with Zyprexa
    - "titrating up to 40mg, see how it goes"

Clozaril is the Gold Standard for TX resistant pts -
Risperdal proven equally effective

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Janssen CME Program

- Bipolar Disorder
  - Atypicals may possess Mood Stabilizing Properties
  - Risperdal 2-3mg/day, 65-85% response rate, mostly as an adjunct to a M.S. (open label reports)
  - Rationale for Risperdal ‘inducing’ mania = pts were withdrawn from their M.S.
  - Zyprexa trials: 48.6% total response vs 24.2% placebo

Monotherapy with an atypical for Bipolar is **NOT AN APPROPRIATE STRATEGY**
Janssen CME Program

• Dementia
  - Risperdal being used 1st line in the US
  - Start at 1/4mg and titrate up to 1 or 2mg
  - Zyprexa 1-8mg/day not superior to placebo, “maybe the dose was too low”
  - Study in elderly schizophrenics showed Zyprexa = Haldol on efficacy and disc rates

Risperdal has by far the most data in elderly -
Dementia and Schizophrenia

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Janssen CME Program

- EPS for Risperdal dose dependent but only above 8mg
- Rationale for *occasional* EPS at lower doses = 10% of pts are deficient in isoenzyme that metabolizes Risperdal
- Zyprexa, superiority to Haldol shown at at lower doses but not 15mg or above
- Seroquel - best EPS profile

**EPS profiles of Zyprexa and Risperdal are similar**

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Janssen CME Program

- Zyprexa, Clozaril, Seroquel = most H1 blockade
- Weight gain has serious consequences - ‘diet modification’ is not a satisfying answer for these pts
- Verbalized that Zyprexa = Clozaril in wt gained, takes 6 mos to plateau
- Risperdal gains take 3 mos to plateau

Zyprexa and Clozaril have similar wt gain profiles - can lead to greater risk of CV disease, diabetes, etc.

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Janssen CME Program

- All antipsychotics have potential to increase prolactin
- Risperdal - no significant correlation with side effects in males or females
- Seroquel and Clozaril least likely to elevate levels - switch to one of them if side effects ‘happen to occur’ with Risperdal

Risperdal has greatest potential to elevate prolactin but most patients will not suffer side effects

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- 85% schizophrenics meet clinical criteria for cognitive impairment
- Cognitive deficits contribute significantly to long term disability (prevent ‘reintegration’)
- Atypicals may provide a primary benefit of improving cognition
- Limited data exists

More studies need to be done, but most impressive data currently is with Risperdal

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<table>
<thead>
<tr>
<th>Division</th>
<th># of reps</th>
<th>Products</th>
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<tr>
<td>Janssen Field 1</td>
<td>500</td>
<td>Sporanox, Propulsid</td>
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<tr>
<td>Janssen Field 2</td>
<td>425</td>
<td>Propulsid, Sporonoxx</td>
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<td>CNS</td>
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<td>Risperdal, Paxil</td>
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<td>Janssen Hosp.</td>
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<td>Sporonoxx, Propulsid,</td>
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<tr>
<td></td>
<td></td>
<td>Duragesic</td>
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*October 14-15, 1998*
Zotepine Profile

Zotepine, Lodopin, Nipolept (Fujisawa, Knoll, Klinge/RPR - Germany)

- D₁, D₂, 5HT₂ antagonist, and norepinephrine uptake inhibitor
- Launched: Austria, Germany, Japan, and South Korea
- Preregistered: France, Spain, Taiwan, and the UK (Mutual recognition process initiated*)
- Indication: Treatment of schizophrenia
- Dose: 150 - 300 mg
- Claims: Statistically superior to chlorpromazine (BPRS), relapse prevention (double blind placebo controlled), with low EPS
- Other: Undergoing clinical trials in Germany for Manic disorders
- Weaknesses: Negative Sx efficacy questionable, prolactin elevation, seizures

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Risperdal Competitive Strategy Session (US)

Threats and Opportunities for Zypraxa

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Risperdal Competitive Strategy Session
Top threats to Zyprexa

- Weight gain
  - Need for framing from outside opinion leaders
  - Acknowledge issue, characterize as class effect, and put it in perspective

- Cognition
  - Complex issue, first address peer to peer
  - Question validity of Janssen claims

October 14-15, 1998
Risperdal Competitive Strategy Session
Top threats to Zyprexa, cont.

- Elderly
  - Janssen effectively using elderly data in market segments that we are not currently pursuing
  - Lilly LTC sales force is out numbered and ineffective

- Cost/Dose
  - Slow onset of action an issue (acute care)
  - Needs to be framed as total cost issue
  - 4mg Risperdal not effective
  - Time/dose study needed for 10 - 15 mg separation
US Affiliate Action Steps

Zytrex's Opportunities

- Higher patient functioning is the major differentiator for Zytrex.
- Market segmentation business case needed - Is the elderly market (22.5%) worth it?
- Tone is crucial - handle objections and get back to selling
- Analysis of strategic pricing options needed
- High strength tablets
Zyprexa Dose
Schizophrenia

Source: IMS Med. Midas

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