# Risperdal's future in the new competitive environment

## 1. Market and Risperdal sales evolution

- 1993 market of antipsychotics is 1.400 mln US$ according to World Review 1993.
- Antipsychotic market is expected to grow (value) with on average 7.3%/year for the next 10 years (Cognos Schizophrenia report, June 1994). Growth is due to introduction of new, better but higher priced antipsychotics such as Risperdal (1993) and other SDAs (≥ 1997).
- Regional average market growth figures are 8.6, 6.6, 5.6 and 7.5 for US, Eu, Japan and Rest respectively. (Cognos Schizophrenia report, June 1994).
- Forecasted Risperdal sales would give Risperdal a value market share of 19%, 47.5% and 42% in 1995, 2000 and 2005 respectively.
- Assuming that the value of conventional neuroleptics will decrease with 2.6%/year (Cognos 94 report), the total estimated sales of new antipsychotics incl. Risperdal and new SDAs is 1,095 and 2,172 mln US$ in 2000 and 2005 respectively.
- Taking the expected Risperdal sales for the year 2000 and 2005 into account, this would only leave 21 mln US$ for the 4 new SDAs combined in 2000 (3 y. after 1st launch)! and 842 mln US$ in 2005. See table 1.
- The figures look somewhat different for the 3 major geographical areas. (See table 2).

*N.America:* The 8.6% annual growth is not sufficient to generate 662 mln US$ Risperdal sales in 2000. The average annual market growth needs to be at least 12% (1993-2000).
At an annual market growth of 20%, there is room for a 50/50 split Risperdal/new SDAs in the year 2000.
Although aggressive, an average 12% annual growth is not impossible for the 1st 5 years after Risperdal launch.
If 25% of old neuroleptic use switches to Risperdal, being on average 4 times more expensive, an achievable objective, the market grows with 75% which is about the growth 93-2000 needed to feed the Risperdal forecast.

*EU:* The 6.6% annual growth allows to reach the 298 mln US$ Risperdal sales in 2000. Here as well, not much room is left for new SDAs. Market growth in Europe as well, however, can be expected to be around 10% (1994-2000).

*AAA:* Even with a modest 5-6% annual growth, the Risperdal forecast of 106 mln US$ in 2000 only represents 42% of the value

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created by this growth. The AAA Risperdal forecast consequently is very conservative.

*Conclusions*

The anticipated growth of the antipsychotic market does not create enough room for the Risperdal sales forecast in N. America and does borderline do so in Europe. Anticipating the launch of 4 new SDAs between 1997 and 2000, the Risperdal forecast in N. America and Europe is very aggressive and aggressive respectively.

In the year 2000, about 50% of all neuroleptic use should have switched to Risperdal and other SDAs to make these sales figures reasonably achievable, corresponding with an annual growth rate of 14%!

It should be noted that schizophrenia represents only 35% of neuroleptic prescriptions so that this growth cannot be generated in the schizophrenia segment only. Aggressive expansion of Risperdal use in other indications is therefore mandatory.

## 2. New competitors

There are 4 SDAs in phase III clinical development at this moment. The 1st launches of these products could be late 1996 (Table 3).
See Table 4 for characteristics although quite some question marks remain, particularly for ziprasidone (Pfizer).

Except in case serious side-effects such as bloodcell toxicity or liver toxicity would appear to be clinically relevant, these products look comparable to Risperdal. Olanzapine is perceived as the most promising, though, because it most closely resembles clozapine (except for agranulocytosis? and much less sedating). A safe clozapine is the product psychiatrists are looking for.

## 3. Critical factors Risperdal vs. new competitors

a. Efficacy
The new SDAs will unlikely be able to claim superiority over Risperdal in positive and/or negative symptoms. There are ways around blunt comparisons to create a "high" efficacy perception, however.
Efficacy in therapy resistant cases is the most obvious one. Olanzapine is being studied in therapy resistant cases. If olanzapine's labeling would include therapy resistant cases apart from 1st line use, it could take quite some market share from Risperdal.

**Scenario:** Risperdal will lose market leadership in ≥ 2000 in the schizophrenia segment in US/Eu down to 30 to 40% of SDA market. Depending on the total market growth (12% / 10% US / Eu to 20% / 10% US / Eu), the Risperdal loss would range between 78 and 220 mln US$ in the year 2000.

*Data on Risperdal in therapy resistant cases are consequently mandatory* (Ongoing). Suitable for additional approval?

All new SDAs are being compared with Haldol for both positive and negative symptoms. In view of a possible superiority over Haldol in negative symptoms or pos. + neg. symptoms combined, this claim may be achievable in the US labeling for those products being compared to different doses of Haldol (olanzapine, ziprasidone?). Superior efficacy Risperdal vs Haldol can be claimed in Eu, not in US. Consequently, particularly in the USA, *additional studies to get a superiority claim over Haldol in schizophrenia or at least neg. symptoms need to be done < Q2, 1996* (is being prepared).
Not having this claim would cost us market share, particularly in the US.

**Scenario:** A Risperdal share down to 30 to 40% of SDA market would give a loss of 49 to 162 mln in a 20% and 12% growing US market respectively.
Is of no relevance outside US.

b. Relapse prevention

Both olanzapine and seroquel are being studied in relapse prevention with the intention to have this as additional indication in the labeling.
This would be a strong argument for long-term use of these products vs Risperdal particularly for formulary / Managed care acceptance. 49% of present US Risperdal sales is paid for by Medicaid.
*A Risperdal IRF in relapse prevention in 1996 is mandatory* (studied ongoing). Still to be investigated whether presently running trials would be sufficient for approval in US.
Risperdal not having this claim vs new competitors having it would cost us market share in the Medicaid segment. This sector will increase in importance in changing US environment.

**Scenario:** 50% of our US Medicaid covered Risperdal sales in schizophrenia represents 58 mln US$ in the year 2000. The Eu impact is more difficult to estimate at approx. 25 mln US$.

c. Negative symptoms

All new competitors particularly evaluate the effects on negative symptoms. Although this may lead to a "claim in negative symptoms" in their labeling, particularly in the USA, this is not to be expected to have a dramatic competitive impact on Risperdal. Although our Risperdal labeling does not mention in most countries an effect on negative symptoms, our labeling does not gainsay it neither. We presently can claim Risperdal's effect on negative symptoms in all countries.

d. EPS

Risperdal's low EPS profile is well recognized in the market. Although olanzapine (ziprasidone) may even have a more convincing low EPS profile than Risperdal, this is unlikely to be clinically relevant and comparative data are unlikely to be in the disadvantage of Risperdal at the optimal dose of 6 ± 2 mg/day.

e. Safety

Any need for blood monitoring because of blood or liver toxicity would make any of these drugs a last resort drug after Risperdal and would limit their impact on Risperdal sales dramatically. Although agranulocytosis has been reported on olanzapine and "non clinically significant" liver enzyme increases on olanzapine, seroquel and sertindole, the extent of these problems is not known at this moment.
Sedation will restrict the use of seroquel to anxious schizophrenics, a small subgroup.
Risperdal is vulnerable because of more pronounced prolactine increase giving rise to sexual dysfunctions and disturbances of menstrual cycle, a sensitive issue which can be exploited by our new competitors. Being dose dependent, the effects of the

new competitors on prolactine cannot be determined as long as their optimal dose has not been determined.

**Scenario:** Effect at the lower range of scenario under a.
Less strong than superior efficacy claim.

f. Pharmaceutical line extensions

*Depot*: Depots represent 17% and 9.5% of antipsychotic prescriptions in schizophrenia in Europe and US respectively. Not being the first SDA with a depot would give marketleadership in this segment to our competitors. At least one (sertindole) SDA-depot is in phase II. The availability of a depot also boosts the use of oral tablets of that particular SDA.

**Scenario:** Risperdal share within depot segment down to 30 to 40% = 11 to 30 mln US$ direct depot sales losses excluding impact on oral sales in 15% / 10% to 20% / 10% US / Eu growing market.

*IM*: About 25-33% of schizophrenic patients are started with an acute IM before switching to oral. The usefulness of a Risperdal IM and other SDA IM formulations is still unclear because of a lack of sedation (except for seroquel) so that conventional neuroleptics may keep their place here or IM benzodiazepines are used for fast sedation, combined with oral SDAs. Although nice to have for Risperdal, not having it is unlikely a **major** competitive disadvantage.

g. Clinical line extensions

***Behavioural Disturbances in Dementia (BDD)*** is the second largest single indication for antipsychotics estimated at 15 to 20% of its use. Value share is lower (± 10%) because of lower doses used. Olanzapine is being studied in BDD. Sertindole and ziprasidone probably as well.

**Scenario:** Risperdal share within BDD segment down to 30 to 40% representing a loss of 22 to 67 mln US$ Risperdal sales in case other SDAs can enter this segment first.

*Other additional indications*:About 50% of antipsychotic prescriptions go to indications other than schizophrenia or BDD.
Schizoaffective disorders, bipolar disorders, borderline psychoses, Tourette's syndrome, mental retardation etc. Risperdal, but also the new SDAs are being explored in schizoaffective disorders.
It should be our objective to consecutively approve Risperdal in the major additional indications as first SDA in each of them.

**Scenario:** A similar calculation for these additional indications combined as for BDD gives losses between 122 and 165 mln US$.

h. Disease state mangement

Both Eli Lilly and Pfizer possess /have cooperation contract with disease state management companies. Being overruled by the competition may have a similar impact as under b. The impact outside US is in this scenario more difficult to estimate. Both companies have major antidepressant drug making the critical mass for disease state management programmes in psychiatry easier to achieve.

## 4. Financial estimations

Table 5 gives an overview of the potential losses in the different scenarios. The present estimations can only give the order of magnitude. Anyhow, it is clear that the risks in certain scenarios are important.

Effects on sales outside N. America / Europe have not been calculated. In view of the modest forecast and relative limited contribution to the total, the order of magnitude of the given estimation would not substantially change.

Risperdal is expected to generate 16 % of the total Janssen Group (new structure) sales in 2000. Every 1% loss on Risperdal sales consequently represents 0.16 % loss in the total Group sales.

## 5. Resources needs

There are 4 aspects in our competitive status vs new competitors.

1. Pre-empt potential additional claims in schizophrenia. This requires large good quality phase IV trials in schizophrenia and at least 1 IRF/NDA (relapse prevention) (therapy resistant?).
2. Approve new indications. This requires at least 2 GCP pivotal trials per indication for at least 3 (BDD, Schizoaffective, bipolar, ...), possibly more IRF/NDAs apart from trials for noice in the smaller indications. Every additional indication approved enhances the entry barrier for our competitors and in the mean time makes their out-of-label promotion more difficult.
3. Approve new formulations. Particularly the depot and IM require full IRF/NDAs comparable to a NCE-IRF/NDA. Other additional formulations require "lighter" IRF/NDAs e.g. liquid, quicksolve, once-daily.
4. Timing. Being second with any of the projects costs market share in that particular segment.

This implies the need for 3 JRF managers in Beerse / 3 in JRF US (1 for schizophrenia, 1 for pharm., 1 for clin. line extensions) and in the other affiliates at least 1 full-time JRF Risperdal manager. None of these requirements are presently fulfilled.

The Risperdal depot / Risperdal BDD IRF/NDA risk already now to come second.
Schizoaffective disorders risk to join this risk.

Ivo Caers
October 1994

**Table 1: Antipsychotics: Market and Risperdal sales evolution**

| | *1993* | *1994* | *1995* | *2000* | *2005* |
|---|---|---|---|---|---|
| Market[1][2] (mln US$) | 1,400 | 1,498 | 1,604 | 2,259 | 3,195 |
| Conventional Neuroleptic sales[3] (mln US$) | 1,392 | 1,364 | 1,328 | 1,164 | 1,021 |
| Anticipated SDA sales (mln US$) | 8 | 134 | 276 | 1,095 | 2,172 |
| Anticipated Risperdal sales[4] (mln US$) | 8 | 185 | 302 | 1,074 | 1,330 |
| % Market share Risperdal | 0.6 | 12.3 | 18.9 | 47.5 | 41.7 |
| "Remaining" other SDA sales (mln US$) | - | - | - | 21 | 842 |

(1) World Review 1993
(2) 7.3% annual growth (Cognos Schizophrenia Report, June 1994)
(3) -2.6% annual growth " "
(4) Actual 1993, EO 1994, POF 1995, 94 Strat. Plan 2000, 2005

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**Table 2: Risperdal sales expectations[1] and anticipated market evolution[2] per geographical area**

| | | *1995* | *2000* | *2005* |
|---|---|---|---|---|
| *N. Am.* | Market | 560 | 846 | 1278 |
| | Conventional | 451 | 395 | 346 |
| | SDAs | 110 | 451 | 932 |
| | Risperdal | 236 | 662 | 815 |
| | "Room for" Other SDAs | (126) | (210) | (117) |
| *EU* | Market | 534 | 735 | 1012 |
| | Conventional | 446 | 391 | 343 |
| | SDAs | 88 | 344 | 669 |
| | Risperdal | 61 | 298 | 381 |
| | "Room for" Other SDAs | 27 | 47 | 289 |
| *AAA* | Market | 440 | 578 | 760 |
| | Conventional | 375 | 328 | 288 |
| | SDAs | 66 | 250 | 472 |
| | Risperdal | 4 | 106 | 116 |
| | "Room for" Other SDAs | 62 | 144 | 356 |

(1) Janssen Group Figures (2) Cognos 1993 report

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**Table 3: Status new Risperdal competitors**

| *Product* | *Company (ies)* | *Status* | *IRF/NDA expected* |
|---|---|---|---|
| Olanzapine (Lanzac™) | Eli Lilly | Ph III | Q4-1995 |
| Seroquel | Zeneca | Ph III | Q4'95-Q1'96 |
| Sertindole | Lundbeck<br>Abbott (US)<br>Shionogi (Japan | Ph III | Q4'95-1996 |
| Ziprasidone | Pfizer | Ph III | Q4-1996 |
| Org 5222 | Organon | Late Ph II | ≥ 1996 |

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**Table 4: Preliminary overview product characteristics new SDAs in function of Risperdal characteristics**

| | ***Risperdal*** | ***Olanzapine*** | ***Seroquel*** | ***Sertindole*** | ***Ziprasidone*** |
|---|---|---|---|---|---|
| Efficacy on Pos. symptoms | | | | | |
| vs Haldol | >[1] | ≥ | ≤ | = | =? |
| vs Risperdal | | = | ≤ | ≤ | =? |
| Efficacy on Neg. symptoms | | | | | |
| vs Haldol | >[1] | > | > | > | > |
| vs Risperdal | | = | = | = | = |
| Efficacy in therapy resistant cases | + | ++? | - | +? | ? |
| Dosing simplicity | + | +(+) | +? | - | + |
| Low EPS vs Risperdal | | ≤ | ≤ | ≤ | = |
| Prolactine S.E. | ++ | - | -? | + | +(+) |
| Liver safety | OK | enzymes↑ | enzymes↑ | enzymes↑ | ? |
| Blood safety | OK | agranulocytosis? | ? | ? | ? |
| Cardiovascular safety | + | +(+) | + | + | ? |
| Anticholinergic S.E. | no | yes | no? | no | no? |
| Sedation | no | no | yes | no | no? |
| Depot | ph.I | ≤ ph.II | ≤ ph.II | ph.II | ? |
| Additional indications | ≤ ph.III | ph.II | - | ph.II | ph.II |
| Company CNS commitment | ++ | ++ | + | +(+) | + |
| Disease Management Programmes | - | + | - | ? | + |

(1) Can presently not be claimed in USA

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**Table 5: Potential impact critical factors on Risperdal sales in year 2000**

| *Competitor attribute* | *Financial impact (mln USD)* | *% of worldwide sales* | *Remarks* |
|---|---|---|---|
| a. Superior efficacy | 78 to 220 | 10 - 20 % | |
| Superior over Haldol | 49 to 162 | 5 - 15 % | US impact only |
| b. Relapse prevention claim | 82+ | 8 % | Particularly in Medicaid sales |
| c. Negative symptoms claim | limited | - | |
| d. Low EPS | limited | - | |
| e. Safety (! prolactine) | 78 - 150 | 10 - 14 % | |
| f. First depot SDA | 11+ to 30+ | 1 - 3 %+ | + is substantial |
| First IM | limited | - | |
| g. First in BDD | 22 to 67 | 2 - 6 % | |
| First in others | 122 - to 165- | 11 - 15% | - because not all indications similarly affected |
| h. Disease state management | 49 to 162 | 5 - 15 % | US impact particularly |

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