Minutes Risperdal Taskforce, Beerse, Dec. 6-7, 1994

Present:	France	Philippe Alfocea / Pierre Quelet
	UK	Jane Griffths
	Japan	Hajime Enjoji / Tetsu Nagase
	USA	Tom Anderson / Heng Wong
	Beerse	Ivo Caers / Raf De Wilde / Philippe Lemmens
		Eric Pauwels / Françoise Rampelberg
Absent:	Canada	Jim Eckhardt
	Germany	Kai Martens

For overview Olanzapine / Seroquel / Sertindole and Ziprasidone, see SAE report

Additional competitive info

Olanzapine

- Eli Lilly is setting up cost of disease study in Germany
- CND study comparing Risperdal - Olanzapine
  . safety & efficacy
  . HE data
  . cognitive function
- Lilly stopped research on Gastro → focus on CNS
- sales rep recruitment in UK (incremental to Prozac)
- NMS case reported (1)
- TD cases reported (3)
- WHO essential drugs list submitted
- 5→10→20 mg Haldol comparison (phase III)
- benefit to M1 receptors antagonism; explored as a benefit
- liver enzymes, drug interactions may be critical
- agranulocytosis in animal (Japan)

Seroquel

- EPS profile similar to chlorpromazine
- Zeneca is doing extensive Market Research (cojoint in Europe / US?)
- sedative

Sertindole

- relapse prevention project, run by Kissling, Germany
- contact patient support groups (Switzerland)
- turnover in clinical research dept. - USA is high
- investigators lack of confidence (dose problems) (ocular tests) - Belgium
- CNS agreement in Germany with Byk Gulden
- Lundbeck is a candidate for take-over

PLAINTIFF'S EXHIBIT 58

Exhibit Caers - 3 08.19.09

EXHIBIT P-58

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Ziprasidone

- cardiovascular safety incl. ECG monitoring vs Risperdal (6, 8, 10 mg) is being studied (UK, Australia)
- comparative trial vs Haldol 5 mg Acute exacerbations in Switzerland
- Pfizer published placebo vs Haldol on cognitive effects
- investigators looking for a new "hook"?
  . safety
  . cognition

Clozapine

- comparative trial vs Risperdal planned in France / Canada
  . maintain Treatment Resistant Patient population
  . negative symptoms
  . EPS (up to 16 mg Risperdal is used)

Amisulpiride

- large clinical studies in Eastern Europe & USA & UK
- licensing USA (?)
- comparative trial vs Risperdal in France (up to 16 mg)
  → looking at positive symptoms

Others

- ORG5222: discontinued worldwide

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SWOT-analysis: Olanzapine / Eli Lilly

Strengths	Weaknesses
- positive + negative symptoms - comparative claims vs Haldol - low EPS - most Clozapine-like product (broad spectrum) - limited prolactin ↑ - *can go to GP's (Prozac) (e.g. in BDD)* - *high CNS commitment* *. Marketing* *. R&D* - *Dis. State Management organisation* - *Intense psychiatry contacts / advocacy groups* - *good FDA relationship* - *aggressive marketeers*	- postural hypot. + titration - strong anticholinergic effects - TD reported (3/300) - sedation (oral) - liver enzymes ↑ - weight gain - *3 y behind Risperdal* - *US marketing = global*
Opportunities	**Threats**
- effective in primary negative symptoms - anxiolytic effect - minimal orthostatic hypotension - effective in schizoaffective - data in treatment resistant patients - BDD claim - relapse prevention claim - sedation IM - D4 story - similar to clozapine - *unsatisfied market* - *co-marketing in Europe? Shering in US?* - *WHO list*	- aplastic anaemia / agranulocysis - no superiority over Haldol - confusion re. dosing - drug interaction - *managing expectations* - *price erosion (competition)* - *Janssen strategy*

standard lettertype = product related
italic lettertype = company-environment related

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SWOT-analysis: Seroquel / Zeneca

Strengths

- low prolactin ↑
- low EPS

- *Stuart Disease State Management*
- *strong consistent developers*
- *global US / Europe / Japanese company*

Weaknesses

- EPS = chlorpromazine
- QT prolongation
- liver enzymes ↑
- sedation (oral)
- need for titration / art.hypotension
- dizziness

- *no CNS franchise / no psychiatric contacts*
- weight gain
- *weak marketeer in US*
- *≥ 3 y behind Risperdal*

Opportunities

- relapse prevention
- sedation IM

- *low expensive SDA (cfr. Remoxipride)*

Threats

- better efficacy of new drugs

- *other Zeneca pipeline products*
- *order of new entries (3rd, 4th?)*
- *Janssen strategy*

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SWOT-analysis: Sertindole / Abbott/Lundbeck

Strengths

- no prolactin ↑
- low EPS
- IM + depot
- low sedation

- *Lundbeck:*
  - *. high CNS commitment*
  - *. "prelapse" program*
  - *. aggressive marketeers*
- *Abbott:*
  - *. experienced in very comp. market*
  - *. valproate in bipolar disorders*
  - *. bundled products*
  - *. good institutional marketing*

Weaknesses

- strong α-lytic
- slow titration
- liver enzymes ↑
- 2 active metabolites
- QT prolongation
- doubt efficacy negative symptoms
- IM not sedative

- *SSRI introduction (Lundbeck)*
- *not global company (Lundbeck)*
- *fragmented launch*

Opportunities

- 1st SDA depot
- schizoaffective

- *could entry before olanzapine*
- *low expensive SDA (remoxipride)*
- *link Byk Gulden*

Threats

- no superiority over Haldol
- interactions

- *new competitors*
- *miscommunication 3 companies*

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SWOT-analysis: Ziprasidone / Pfizer

Strengths	Weaknesses
- no dose titration - low α-lytic - first episode patients - *Dis. State Management* - *CNS commitment* - *aggressive spenders* - *centralized clinical development* - *project management approach* - *speed to market*	- dose related EPS - χnd SDA - *rich pipeline* - *domestic / non-domestic organisation*
Opportunities	**Threats**
- schizoaffective - equal efficacy = Risperdal - development IM - anxiolytic / antidepressant effects - studies in negative symptoms - data in therapy resistant patients - BDD (no orthostatic / anticholinergic) - cardiovascular safety	- not superior to Haldol - *prize competition*

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italic lettertype = company-environment related

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SWOT-analysis: Risperdal

Strengths	Weaknesses
- 1st SDA (pos. + neg. + low EPS) - not sedative - long-term experience . efficacy . safety	- not sedative (acute) - high prolactin ↑ - weight gain - low impact in acute cases
Opportunities	**Threats**
- schizoaffective - BDD - relapse prevention - HE data - liquid - once-daily - effective in: . 1st period . therapy resistant - other patient populations - new class = standard - Risperdal + benzodiazepines (acute)	- *room for better than Risperdal* - *new competitors* - *new competitor vs Risperdal comparisons* - *slow development* - *low unit penetration* - *CNS pipeline products*

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Advantages / Disadvantages new SDA's vs Risperdal

Olanzapine = 0
Seroquel = sq
Sertindole = st
Ziprasidone = z

Advantages	o	sq	st	z	Disadvantages	o	sq	st	z
low / no prolactin ↑	x	x	x	?	liver enzyme ↑	x	x	x	?
superiority (efficacy)	?	o	o	o	blood dyscrasias	?	o	o	o
HE / outcome data	x	?	?	?	sex. dysfunction	o	o	x	o
lower side effects	?	?	?	?	anticholinergic	x	o	o	o
lower EPS / TD	?	o	o	o	contacts with OL	x	o	x	o
titration	o	o	o	x	TD	x	?	?	?
QT	?	o	o	?	titration	o	o	x	o
sedation (acute)	x	x	o	o	complex pharmaco-kinetics (metabolites)	o	o	x	?
BDD data available	o	?	?	?	drug interactions	?	?	x	?
Treatment Resistant	x	x	?	?	low US impact	o	x	?	o
line extensions	x	?	x	x	too high expectations (clozapine like)	x	?	o	o
broader receptor binding	x	o	o	o	late in Clin. Dev.	o	x	o	x
resources human and $	x	?	?	x					
relapse prevention	x	x	x	x					

x = yes
? = possible but not known
o = no / unlikely

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Major competitors' disadvantage		Minor			Comparable to Risperdal		Minor		Major competitors' advantage over Risperdal	
0	1	2	3	4	5	6	7	8	9	10
						no titration				sup. N / pos vs Risp.
blood monitoring (liver/blood)			too high expectations		low SE		low prolactin ↑		Sup. N / Pos. vs Haldol	
		sedation chronic/elderly				sedation acute		sup. neg. vs Haldol		efficacy prim. neg. symptoms
	Clozapine price			quicksolve				efficacy treatment resistant		
		high TD		liquid		no QT ↓		ahead in BDD		better HE data
							ahead with depot		Relapse prevention claim Remoxipride price	
				premium price vs Risperdal		IM aucte schizoaffective (US)				schizoaffective outside US
				sexual dysfunction anticholinergic image, OL, advocacy group contacts drug interaction						continued resources

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Act as a market leader / global strategies to maintain leadership

What the market leader should and should not do	What the follower should and should not do to become leader
First (market leader)	***Second and consecutive***
+	+
- close follow-up early adaptors / go beyond early adaptors with adapted strategy in different types of target group - act pro-actively (be first in all line extensions) (SDA's / reimbursement) - creates market + define own role so that → others behave → stability in market - continue to redefine the market if necessary - consistent publication strategy, control editorials, etc. = bench market . price . spending . development - continuous commitment to OLs advocacy groups + other clients - think broadly incl. non-traditional thinking - increase entry barrier - behave as a leader (attitude) - aggressive posture - maintain global strategy - come with line extensions at time of launch second	- behave as a market leader - position as breakthrough product - lack of any respect for market leader / aggressive marketing - top to bottom commitment from company to achieve market leadership - take leadership in line extensions pharmaceutical + new indications - explore high risk and huge areas others have not entered - guerilla war approach
-	-
- re-active in line extension + strategy (always second) - stay with early adaptors - change in strategy when others come in - don't compare just on product characteristics - still in niche position (< 15% in psychiatric units)	- over-promise / too high expectations - wrong pricing - no clear positioning vs market leader - don't rely on just promotional spending - no extensive pre-marketing - rely on class effects re. off-label use - under-estimate the leader

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Olanzapine: Potential Positioning

- the most effective first-line (atypical) therapy for full range of symptoms in schizophrenia and other psychotic disorders
  . multi-receptor, not SDA
  . QoL
  . long-term
  . Clozapine-"like"
  . easy to use antipsychotic "user friendly"
  . first-line atypical

Seroquel: Potential Positioning

- first-line atypical antipsychotic

or

- "Risperdal-like" positioning
  . similar efficacy
  . lower price ?
  . less prolactin ↑
  . not anticholinergic

or

- schizophrenia with anxiety

Sertindole: Potential Positioning

- Risperdal like positioning
  + differentiate as health care supplier, partner in treating psychosis
- only SDA depot "Prelapse"
  (price = or < Risperdal)

Ziprasidone: Potential Positioning

- positioning "safer" Risperdal
  (focus on cardiovascular, prolactin, cognition)
  (simple, safe, "user-friendly Risperdal like" antipsychotic)
- Potential in elderly incl. BDD

Risperdal Strategy

Issues

- maximize unit share before new competitors come in
- prevent a reimbursement backlash or maintain reimbursement long-term
- create "broad use" perception
- develop essential line extensions
- develop first-line use "in practice"
- identify key issues that are communicated to Senior Mgmt regularly

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'Tactics to drive unit share asap

- expand target group to schizophrenia treatment group (nurses, social workers, advocacy groups, ...)
- heavy investment in medical education, PR, symposia, ...
- enhance training re. consultative sell, micro-marketing
- enhance value for money perception

  . value added programs
    - EPS detection for nurses / GP's
    - out hospital follow-up
    - guidelines on correct use of antispychotics incl. Risperdal
    - use WPA program (for non-psychiatrists)
    - program for consumers / care giver re. NEW schizophrenic patients (Risperdal users groups) (WHO project!) (Info exchange!)
    - program for family newly diagnosed schizophrenics
    - GP orientation programs re. schizophrenia

  . enhance perceived value of the drug
    - consistent dominant approach
    - keep enhancing problems schizophrenia in society
    - case studies

  . hospital pharmacy programs (explore their needs)
    - schizophrenia
    - health economy in general
    - health economy data on Risperdal
    - enhance their self esteme (emotional approach)

- publications on:
  . swiching
  . anything positive on Risperdal in schizophrenia
  . elderly schizophrenia / young / late-elderly
  . different races
  . primary / secondary negative symptoms + Risperdal
- milk the existing data → publications (analysis = present gap)
- SDA concept + make atypical a bad word
  . publications + in publication SDA re. others
  . consensus pannel(s)
  . MSL tactics to have it implemented
- develop a Risperdal patient register
  . publications
  . PR

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Additional topics

- Depot
  . 1 injection / 2 weeks is OK
  . max. dose to be developed: TBD in MR (ongoing in UK / US / CDN)

- BDD
  . yes for additional scored 0.5 mg tablet
  . ouctome data are being included in studies
  . no need for separate trademark

- AIR multiclient market study on Risperdal
  . Beerse buys 1st country available 50/50 budget (UK / Germany?), cost £ 10,000/country
  . distribute + purchase other countries if studies would be done. Janssen does not stimulate start of study by ordering now. Coordinator = Raf De Wilde, Beerse

Eric Pauwels / Ivo Caers
December 14, 1994

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Maximize unit penetration

Clinical / Product development

Schizophrenia

1 efficacy in primary negative symptoms
 . long-term outcome, link it to efficacy on negative symptoms
 . what is olanzapine doing in primary negative symptoms (do they split it?; if yes, how do they do? Canada, UK, US, deadline before 15/1/95)
 . N. Andreasen trial Risperdal in US
 . "Möller"-type analyses of existing data other than Marder trial/ meta-analysis?
 . explore creative clinical approaches Risperdal in negative symptoms
 . case reports on negative symptoms

2 Superior over Haldol (positive and/or negative symptoms: ! US)
 . objective: have superiority in the US labeling
  - 1 or 2 trials?
  - results INT-6?
  - deadline end Q1 '95 to start 1st US trial
  - centers of excellence!?

3 Efficacy in treatment resistant
 . possible to have in the labeling? (including therapy resistant), how? to check with Regulatory
 . running trials Risperdal are OK for perception creation, would be sufficient to include in labeling if positive → IRF if we would like so (Regulatory?)

4 HE / Outcomes
 . QoL + other clinically / family / care giver relevant outcomes
 . 3-5 year study re. Risperdal changing the outcome?

5 relapse prevention
 . check INT-6 / GBR-13: enough for labeling? Regulatory) Non-US / US
 . IRF to be filed worldwide: Q2 '95

6 prolactin
 . evaluate clinical relevance S.E.
  - vs placebo!
  - vs reference compounds
  ⇒ no clinical relevance story → publish shortly before

7 first episode patients, more open data, conservative dosing → publish
 . comparative long-term trial incl. outcome!

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8 sedation issue
. publish data anti-sedation story
. studies: if needed, add benzodiazepines
. consultancy group
- publish
- PR (sedation: family members)
sedation ↔ effect on negative symptoms

9 anticholinergic
. muscarinic effect = positive means what? explore with AER
. anticholinergic SE in elderly!
. cognitive functioning Risperdal vs anticholinergic drugs

Formulations

- depot
. determine what is needed from regulatory point of view
. fast track development

- IM
. safety concerns cardiovascular (wait for RIS-INT-2 results)
. explore in MR impact titration (running in UK / US / CDN)

- Quicksolve
. develop ASAP once feasibility is done (? taste)
. explore which strengths: TBD

- Transdermal patch
. start acceptability study in schizophrenia / BDD: TBD

Other indications

- schizoaffective (non-US countries)
. what trials are needed for labeling?
. follow-up with affiliates on regulatory requirements
. US trial useful for regulatory purposes outside US?

- BDD
. US trial to begin end of Q1 '95 regardless of FDA contact
. HE outcomes / QoL
. Next taskforce on Addtional marketing needs

- mental retardation
Tourette's syndrome
Autism
marketing to determine potential value → priority + Y / No for IRF

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