zyprexa
Olanzapine

Lilly

EXHIBIT 6
PAGE 1 OF 22

ZYPREXA
the novel psychotropic

ZYPREXA is the only psychotropic agent approved for all of the following:

- Short-term treatment of bipolar mania
- Short-term treatment and maintenance of treatment response in schizophrenia

Favorable safety profile

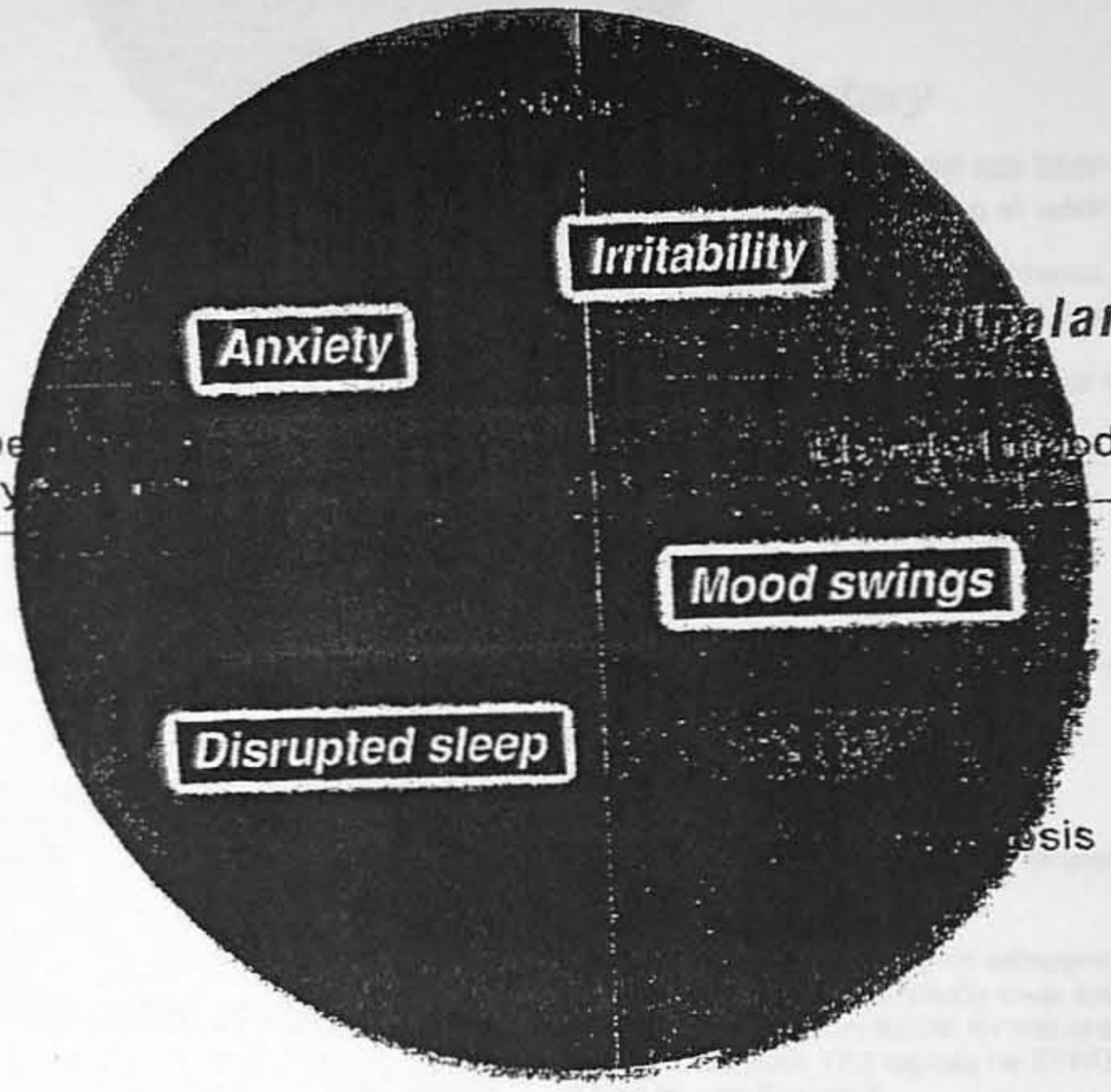
Mood

- Extrapyramidal symptoms (EPS) comparable to placebo
  - In only one analysis of a placebo-controlled study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo
- Effect on prolactin comparable to placebo
  - In 6-week, acute-phase trials involving schizophrenia patients, modest elevations of prolactin were seen, although mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo. A small number of patients experienced asymptomatic elevations of hepatic transaminase; none of these patients developed jaundice or drug-induced hepatitis.
- Low potential for harmful drug interactions
- No significant change in QT interval compared to placebo
  - No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials
- No routine blood monitoring

5 years on the market, used by more than 8 million patients worldwide

ZY 4036 88

EXHIBIT 6
PAGE 2 OF 22



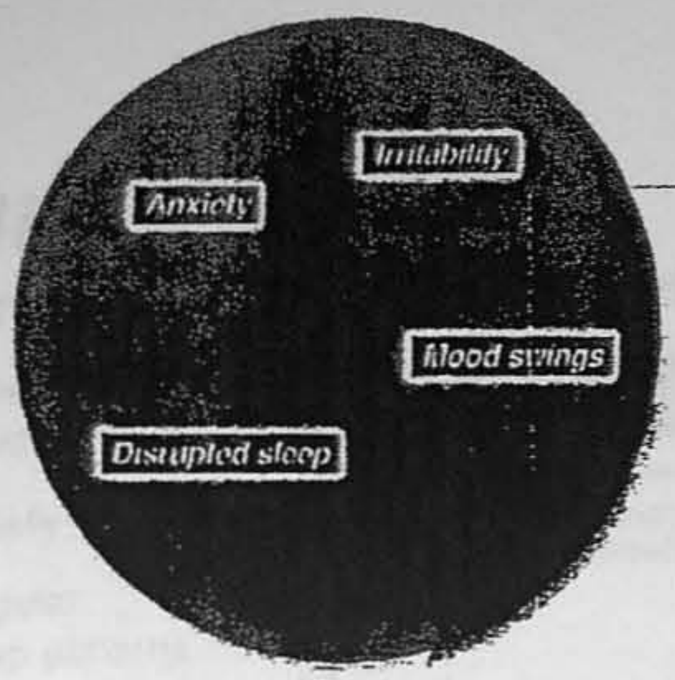
Schizophrenia

ZY 4036 89

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.

Zyprexa
Olanzapine

EXHIBIT G
PAGE 3 OF 22



- Change in appearance
- Decreased energy
- Decreased concentration

Donna

Single mom in her mid-30s, presents in drab clothing and seems ill at ease

"I feel so anxious and irritable lately."

History

- Reports she has been sleeping more than usual, has trouble concentrating at work and at home
- Several appointments earlier, she was talkative, elated, and reported little need for sleep
- You have treated her with various medications including antidepressants

Favorable safety profile

- **Incidence of EPS significantly lower than Risperdal® (risperidone)[11]**
  - Incidence of treatment-emergent extrapyramidal symptoms (EPS) was significantly lower than Risperdal (12.5% for ZYPREXA vs 22.3% for Risperdal; $P=.034$, Mean modal doses: 17.2 mg/day for ZYPREXA, 7.2 mg/day for Risperdal)
- **Incidence of prolactin elevation significantly lower than Risperdal[11]**
  - Potential complications of prolactin elevation may include sexual dysfunction, amenorrhea, galactorrhea, gynecomastia, and risk of osteoporosis[2-4]
- **Pregnancy category C**
  - No evidence of teratogenicity was observed in preclinical trials; there are no adequate and well-controlled trials with ZYPREXA in pregnant women

1 See Study 2 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1996;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):876-881.

ZY 4036 90

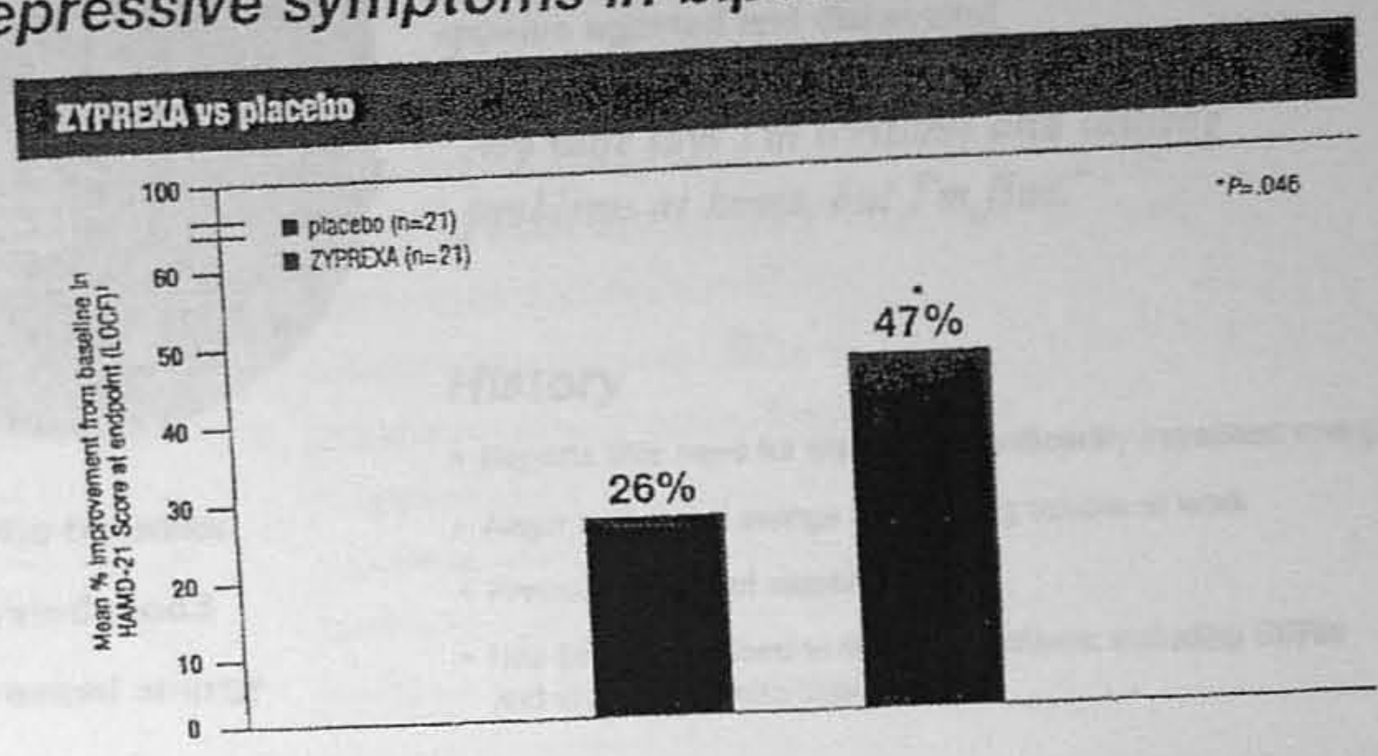
For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Risperdal or Depakote, see manufacturers' package inserts.

EXHIBIT G
PAGE 4 OF 22

Reliable...

Improves depressive symptoms in bipolar manic or mixed patients

- Depressed mood
- Anxiety
- Irregular sleep patterns



Improvement compared with placebo at week 3 in manic and mixed patients with substantial depressive symptoms (defined as HAMD≥20)

1 HAMD-21 is Hamilton Rating Scale for Depression, consisting of 21 items.

LOCF is Last Observation Carried Forward.

See Studies 3 and 4 on pages 18-20 for Methodology and Study Limitations.

ZYPREXA is not approved for the treatment of bipolar depression

Works as early as day 2

ZYPREXA was statistically significantly better (LOCF) in Y-MRS Total Score[1] compared with Depakote® (divalproex sodium) (P=.031) as early as day 2

Mean modal doses were 17 mg QD for ZYPREXA and 1400 mg BID or TID for Depakote

1 Y-MRS is Young Mania Rating Scale, consisting of 11 items.

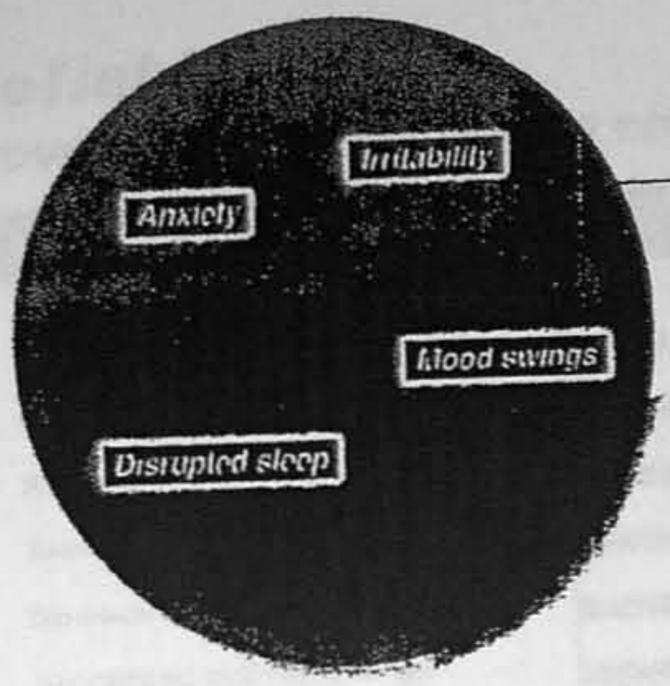
Y-MRS Total Score was measured at days 1, 2, 3, 4, 5, 6, 7, 14, and 21 (endpoint).

See Study 5 on pages 18-20 for Methodology and Study Limitations.

Simple...

Once-daily dosing at bedtime

ZYPREXA®



- Erratic behavior
- Elevated mood
- Increased energy

Mark

Middle-aged male brought in by his wife, appears agitated and disheveled

"My wife says I'm irritable and causing problems at home, but I'm fine."

History

- Reports little need for sleep and significantly increased energy
- Anger and mood swings are causing trouble at work
- Previous history of alcohol abuse
- Has been prescribed various medications, including SSRIs and anxiolytics, with little success

Favorable safety profile

- No black-box or bolded warnings
- No routine blood monitoring required
- Incidence of prolactin elevation significantly lower than Risperdal® (risperidone)[1]
  - Potential complications of prolactin elevation may include sexual dysfunction, amenorrhea, galactorrhea, gynecomastia, and risk of osteoporosis[2-5]

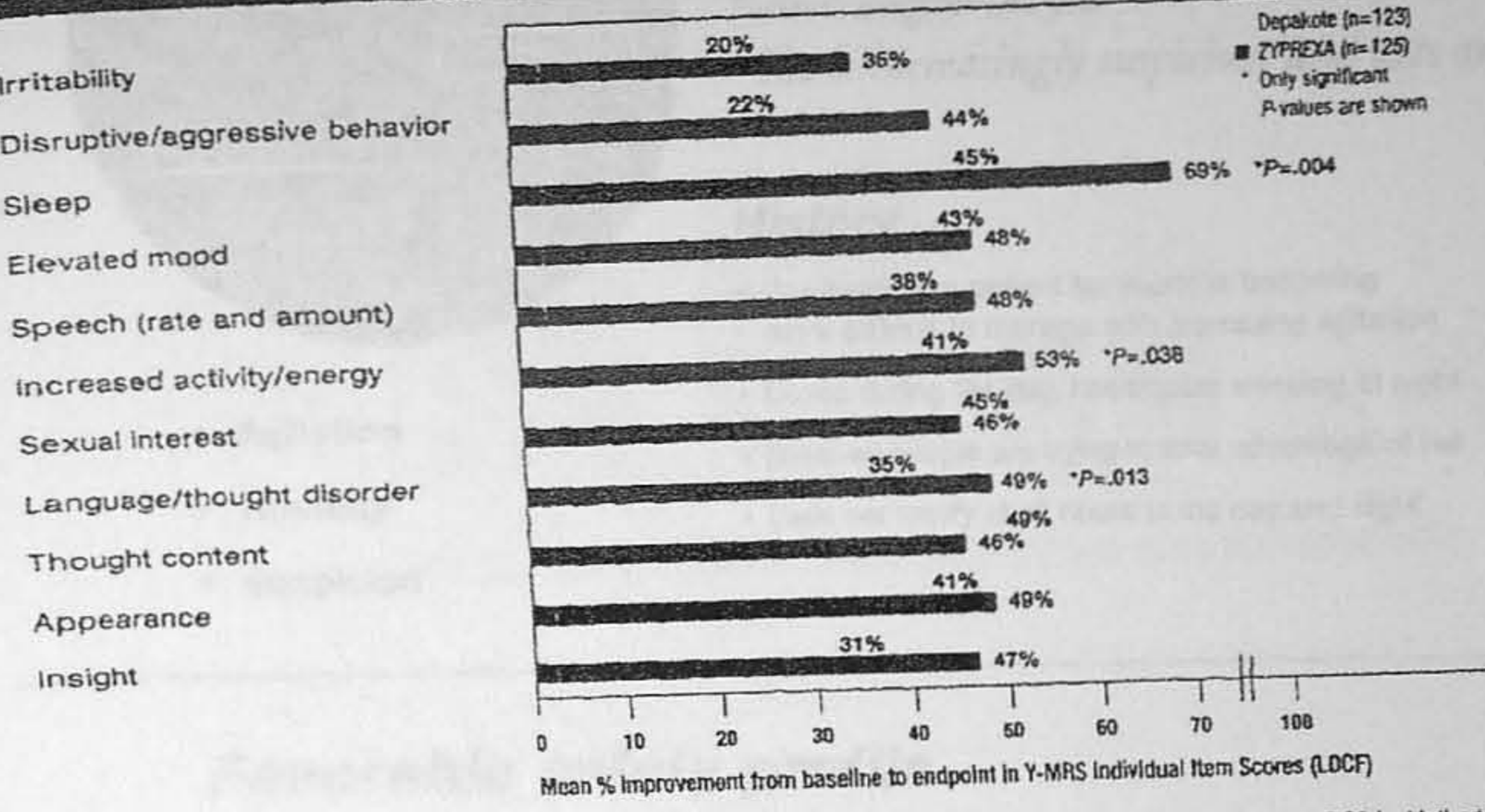
1 See Study 2 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1996;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):875-881.

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Risperdal or Depakote, see manufacturers' package inserts.

Reliable...
Proven effective in treating complicated mood symptoms in bipolar mania[1]

ZYPREXA vs Depakote® (divalproex sodium)



[1] See Study 5 on pages 18-20 for Methodology and Study Limitations.

Works as early as day 2

ZYPREXA was statistically significantly better (LOCF) in Y-MRS Total Score[2] compared with Depakote (*P*=.031) as early as day 2

[2] Y-MRS Total Score was measured at days 1, 2, 3, 4, 5, 6, 7, 14, and 21 (endpoint).

See Study 5 on pages 18-20 for Methodology and Study Limitations.

Simple...
Once-daily dosing at bedtime

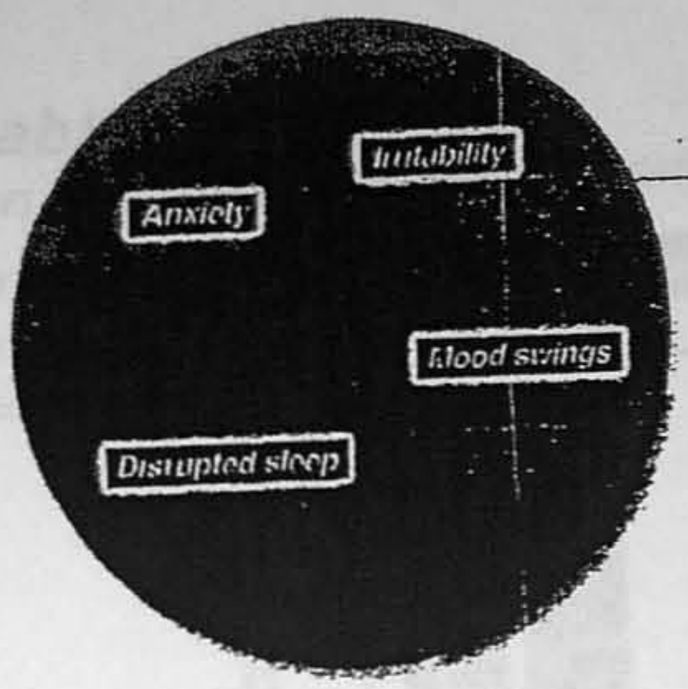
- Reliable efficacy
- Favorable safety
- Simple dosing

ZY 4036 93

zyprexa Olanzapine

Mark

EXHIBIT G
PAGE 7 OF 22



Martha

Widow, living independently near her family

Patient's daughter tells you:
"She is increasingly suspicious and gets angry easily."

History

- Has been your patient for years; is becoming more difficult to manage with increasing agitation
- Dozes during the day, has trouble sleeping at night
- Believes people are trying to take advantage of her
- Calls her family at all hours of the day and night

- **Agitation**
- **Hostility**
- **Suspicion**

Favorable safety profile

- **Low potential for harmful drug interactions**
- **Low potential for anticholinergic side effects†**
  - Incidence of serious anticholinergic events not statistically different from placebo in schizophrenia trials
- **Incidence of EPS significantly lower than Risperdal® (risperidone)‡[1]**
  - Incidence of treatment-emergent extrapyramidal symptoms (EPS) was significantly lower than Risperdal (12.5% for ZYPREXA vs 22.3% for Risperdal; *P*=.034. Mean modal doses: 17.2 mg/day for ZYPREXA, 7.2 mg/day for Risperdal)

† See Study 1 on pages 18-20 for Methodology and Study Limitations.

‡ See Study 2 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. J Clin Psychopharmacol. 1997;17:407-418.

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Risperdal, see manufacturer's package insert.

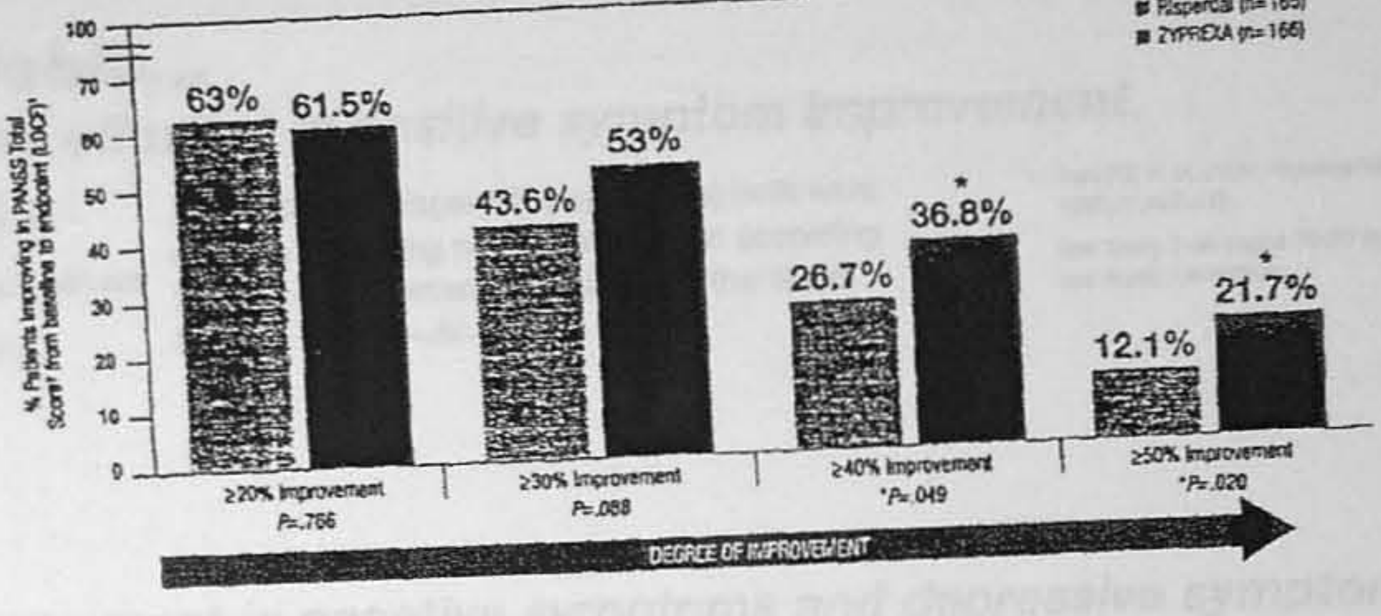
ZY 4036 94

EXHIBIT 6
PAGE 8 OF 22

Reliable...
Proven effective in total symptom improvement

- Hostility
- Anxiety
- Suspiciousness

ZYPREXA vs Risperdal in patients with schizophrenia



A significantly greater percentage of patients treated with ZYPREXA achieved an improvement of ≥40% in PANSS Total Score as compared with Risperdal-treated patients'

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
† PANSS is Positive and Negative Syndrome Scale, consisting of 30 items.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

Simple...
Once-daily dosing at bedtime

- Reliable efficacy
- Favorable safety
- Simple dosing

ZY 4036 95

zyprexa
Olanzapine

EXHIBIT 6
PAGE 9 OF 22

ZYPREXA is the only agent indicated for both bipolar mania and schizophrenia

Reliable...

Proven effective in positive symptom improvement

- Delusions
- Suspiciousness
- Hostility

ZYPREXA and Risperdal® (risperidone) both were effective in treating positive symptoms according to mean improvement in PANSS Positive Score (32% vs 31%, *P*=.654)[1]

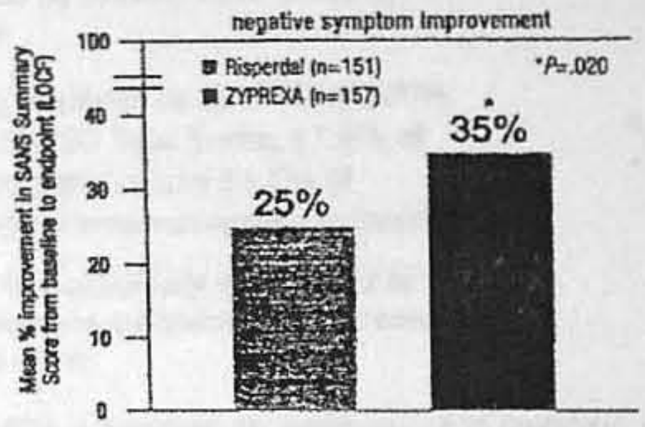
1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

Improvement in negative symptoms and depressive symptoms[1]

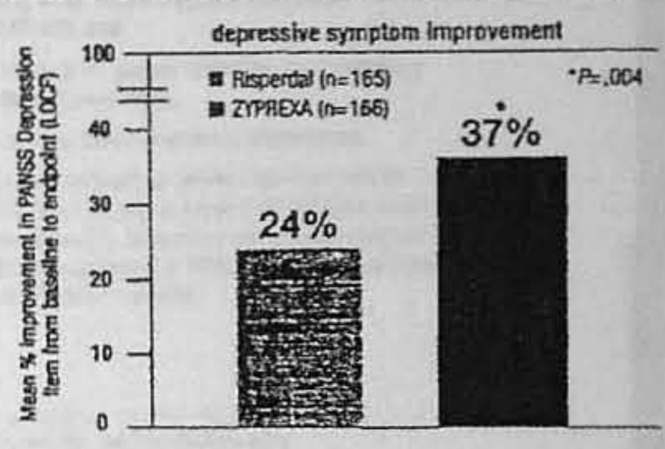
- Lack of motivation
- Social withdrawal
- Sadness
- Hopelessness

ZYPREXA vs Risperdal



ZYPREXA was significantly more effective than Risperdal in treating negative symptoms

ZYPREXA vs Risperdal



ZYPREXA was significantly more effective than Risperdal in improving depressive symptoms associated with schizophrenia

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

SANS is Scale for Assessment of Negative Symptoms, consisting of 24 items.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

ZY 4036 96

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Risperdal, see manufacturer's package insert.

EXHIBIT 6
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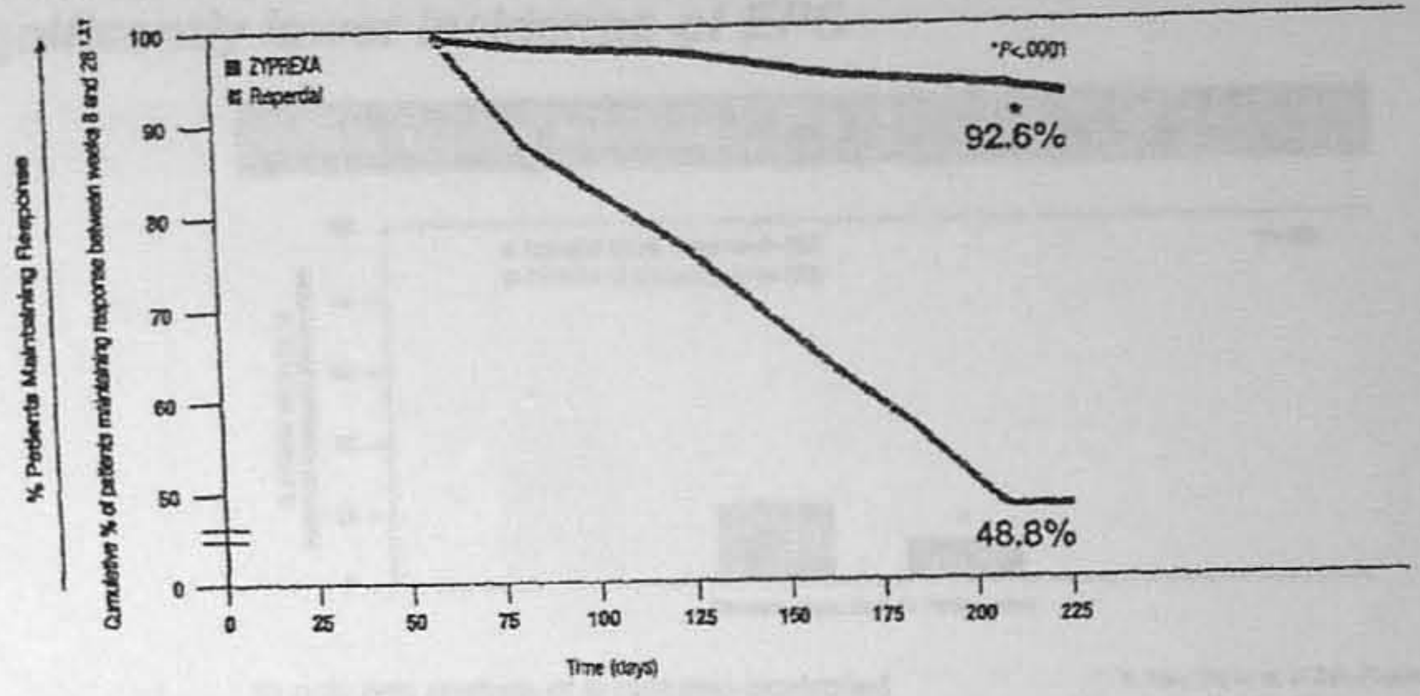
Superior maintenance of treatment response for patients achieving ≥40% improvement

ZYPREXA vs Risperdal



Relapse measured by PANSS Total Score at endpoint (LOCF)†

When measuring response as defined by ≥20% improvement in PANSS Total Score, 87.9% of ZYPREXA-treated patients and 67.7% of Risperdal-treated patients maintained response

Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

2. Data on file, Lilly Research Laboratories.

† Response defined as ≥40% improvement in PANSS Total Score at week 8 (ZYPREXA n=44, Risperdal n=37). Symptom worsening defined as ≥20% worsening in PANSS Total Score plus CGI-S ≥3 after 8 weeks.

ZYPREXA is approved for maintenance of treatment response in schizophrenia

- Reliable efficacy
- Favorable safety
- Simple dosing

ZY 4036 97

Zyprexa Olanzapine

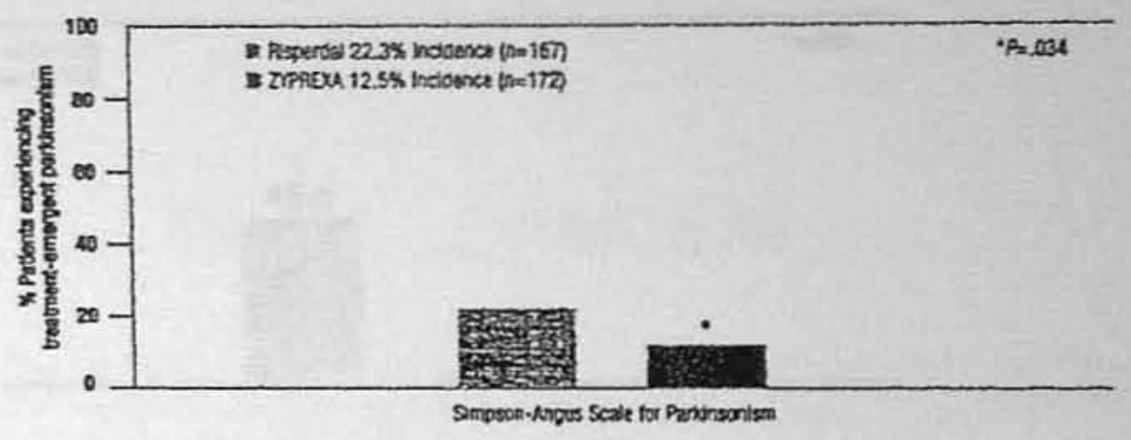
ZYPREXA vs Risperdal

EXHIBIT 6
PAGE 11 **OF** 22

ZYPREXA is the only agent indicated for both bipolar mania and schizophrenia

Significantly lower incidence of EPS

ZYPREXA vs Risperdal® (risperidone)



In only one analysis of a placebo-controlled study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo

Mean modal dose was 17.2 mg/day for ZYPREXA and 7.2 mg/day for Risperdal

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-408.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

EPS symptoms include:

- tremors
- rigidity
- spasms
- restlessness
- inability to sit still

ZY 4036 98

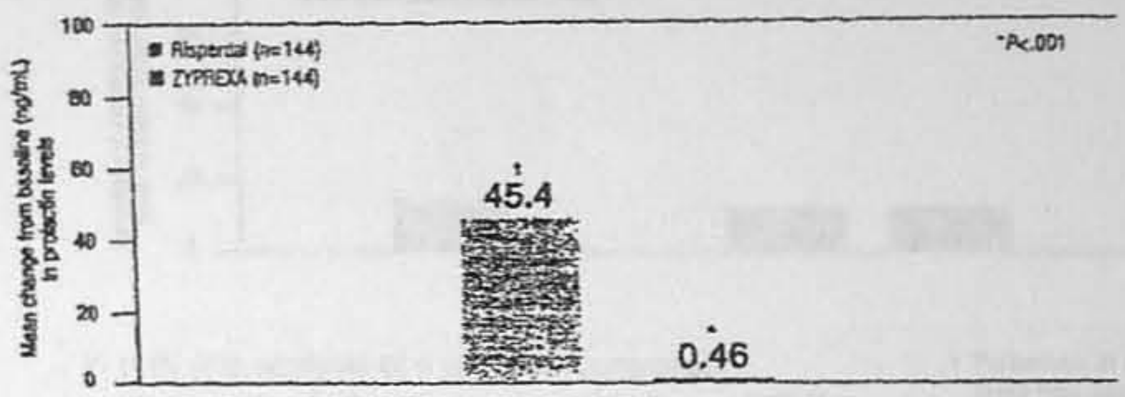
For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Risperdal, see manufacturer's package insert.

Significantly lower incidence of prolactin elevation[1†]

Potential consequences of hyperprolactinemia:

- Sexual dysfunction[2,3]
- Amenorrhea[3,4]
- Galactorrhea[3,4]
- Gynecomastia[3]
- Risk of osteoporosis[4,5]

ZYPREXA vs Risperdal® (risperidone)



ZYPREXA induced significantly lower prolactin elevations vs Risperdal (0.46 ng/mL, 45.4 ng/mL)[1]

Modest elevations in prolactin were seen with ZYPREXA in acute-phase trials (incidence, 34% vs 13% with placebo). However, mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo.[6]

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1995;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):876-881.
6. Data on file, Lilly Research Laboratories.

† Upper limit of normal prolactin levels for males, 18.77 ng/mL; for females, 24.2 ng/mL.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

- Reliable efficacy
- Favorable safety
- Simple dosing

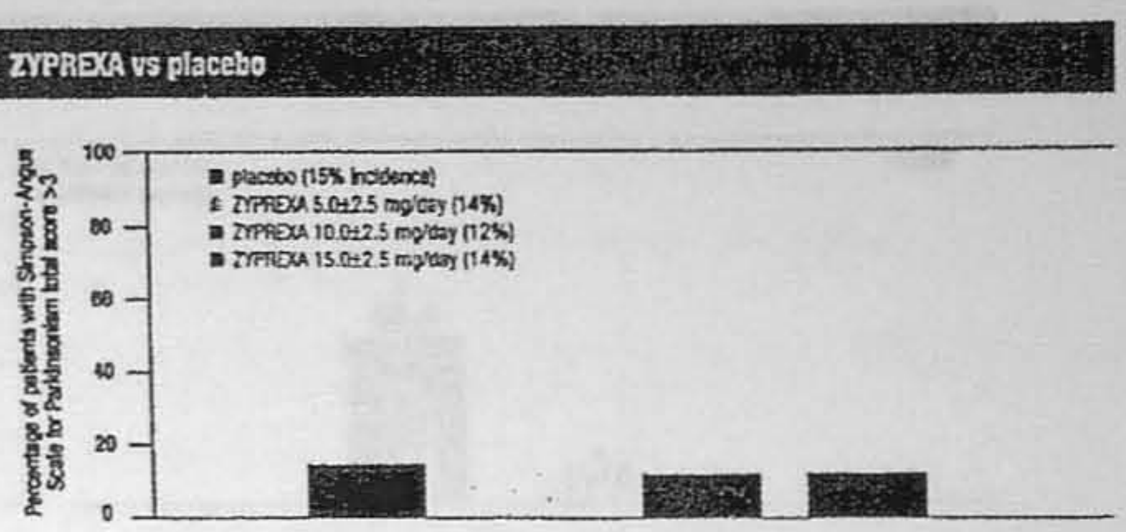
ZY 4036 99

Zyprexa® Olanzapine

Favorable safety profile

Treatment-emergent EPS comparable to placebo at all dose ranges[†]

ZYPREXA vs placebo



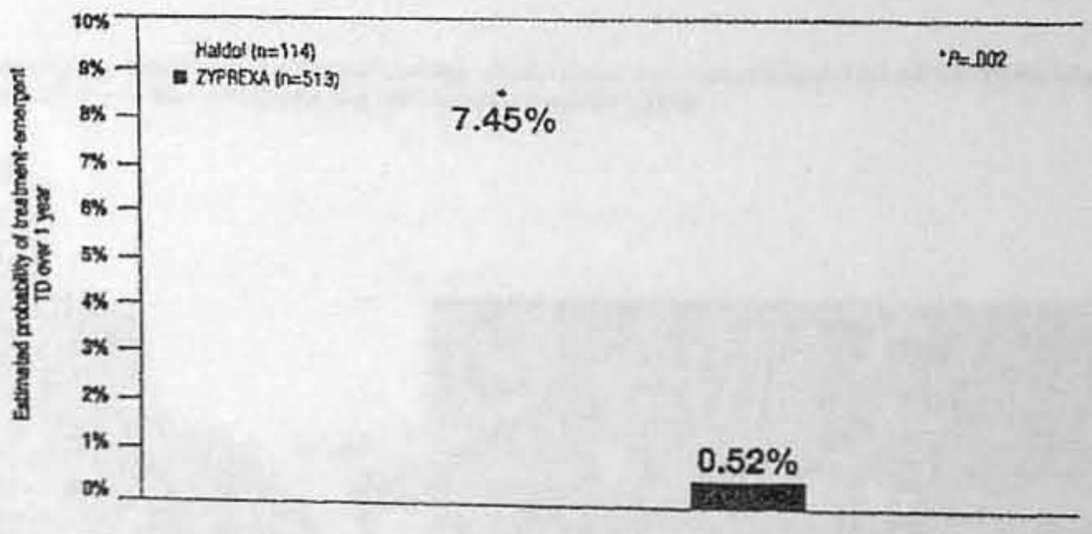
In only one analysis of a placebo-controlled schizophrenia study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo

† Percentage of patients with Simpson-Angus Scale total score >3. No statistically significant differences vs placebo.

See Study 1 on pages 18-20 for Methodology and Study Limitations.

Incidence of tardive dyskinesia (TD) significantly lower than Haldol

ZYPREXA vs Haldol® (haloperidol)



Projected incidence of treatment-emergent TD over 1 year in schizophrenia patients treated with ZYPREXA was significantly lower than in those treated with Haldol[††]

When these data were extended for a total of 700 days, the incidence with ZYPREXA remained low

Prescribing should be consistent with the need to minimize the risk of TD

1. Beasley CM, et al. *Br J Psychiatry*. 1999; 174:23-30.

†† Estimated 1-year risk following an initial 6-week observation period.

See Study 7 on pages 18-20 for Methodology and Study Limitations.

ZY 4036 100

EXHIBIT 6
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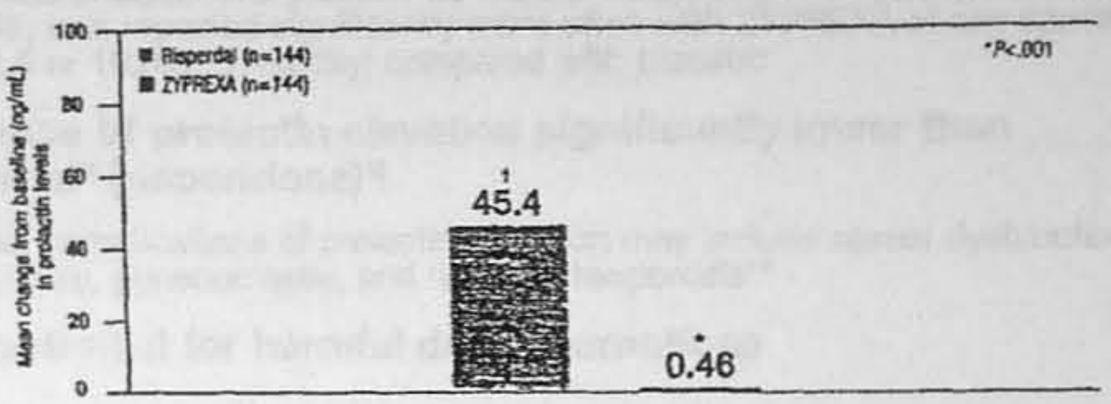
Significantly lower incidence of prolactin elevation[1†]

Potential consequences of hyperprolactinemia:

- Sexual dysfunction[2,3]
- Amenorrhea[3,4]
- Galactorrhea[3,4]
- Gynecomastia[3]
- Risk of osteoporosis[4,5]

ZYPREXA vs Risperdal® (risperidone)



ZYPREXA induced significantly lower prolactin elevations vs Risperdal (0.46 ng/mL, 45.4 ng/mL)[1]

Modest elevations in prolactin were seen with ZYPREXA in acute-phase trials (incidence, 34% vs 13% with placebo). However, mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo.[6]

1. Tran PV, et al. *J Clin Psychopharmacol.* 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs.* 1998;10(3):209-222.
3. Marken PA, et al. *Clin Pharm.* 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull.* 1996;22(3):447-454.
5. Ataya K, et al. *Fertil Steril.* 1988;50(6):876-881.
6. Data on file, Lilly Research Laboratories.

† Upper limit of normal prolactin levels for males, 18.77 ng/mL; for females, 24.2 ng/mL.

See Study 2 on pages 18-20 for Methodology and Study Limitations.

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Haldol or Risperdal, see manufacturers' package inserts.

- Reliable efficacy
- Favorable safety
- Simple dosing

Side effect profile

ZY 4036 101

zyprexa® Olanzapine

EXHIBIT 6
PAGE 15 OF 22

Favorable safety profile

- **Incidence of extrapyramidal symptoms (EPS) comparable to placebo[‡‡]**

  In only one analysis of a placebo-controlled study, only one specific form of EPS, akathisia, was reported significantly more often with ZYPREXA at any specific dose (10.0±2.5 or 15.0±2.5 mg/day) compared with placebo

- **Incidence of prolactin elevation significantly lower than Risperdal® (risperidone)[1,5]**

  Potential complications of prolactin elevation may include sexual dysfunction, amenorrhea, galactorrhea, gynecomastia, and risk of osteoporosis[2-5]

- **Low potential for harmful drug interactions**

- **Low potential for anticholinergic side effects[‡]**

  Incidence of serious anticholinergic events not statistically different from placebo in schizophrenia trials

- **No black-box or bolded warnings**

- **No routine blood monitoring required**

- **Pregnancy category C**

  No evidence of teratogenicity was observed in preclinical trials; there are no adequate and well-controlled trials with ZYPREXA in pregnant women

- **The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled clinical trials for acute mania was somnolence (35% vs 13% for placebo)[‖]**

- **Potential for increased appetite and/or weight gain**

  Early reports suggest behavioral and adjunctive pharmacological strategies can blunt/reduce weight gain[6]

‡ Based on percentage of patients with Simpson-Angus Scale Total Score >3. No statistically significant differences vs placebo.

† See Study 1 on pages 18-20 for Methodology and Study Limitations.

§ See Study 2 on pages 18-20 for Methodology and Study Limitations.

‖ In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation. See Studies 3 and 4 on pages 18-20 for Methodology and Study Limitations.

1. Tran PV, et al. *J Clin Psychopharmacol*. 1997;17:407-418.
2. Hamner MB, et al. *CNS Drugs*. 1996;10(3):209-222.
3. Marken PA, et al. *Clin Pharm*. 1992;11:851-856.
4. Halbreich U, et al. *Schizophr Bull*. 1996;22(3):447-454.
5. Ataya K, et al. *Fertil Steril*. 1988;50(6):878-881.
6. Adapted from: Wirshing DA, et al. *J Clin Psychiatry*. 1999;60(6):358-363.

For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information. For safety information on Risperdal, see manufacturer's package insert.

Simple dosing

ZYPREXA tablets

- Once-daily dosing, with or without food
- Any time of day
- No mandatory titration
- Available in 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets for flexible dosing

ZYPREXA® Zydis® (Olanzapine) Orally Disintegrating Tablets

Where clinically indicated (for example, patients who have difficulty swallowing pills, those who cheek or spit their medication)

- Disintegrates rapidly in the mouth
- No crushing pills
- No difficult liquid dosing
- Available in 5- and 10-mg tablets

Phenylketonurics: ZYPREXA Zydis contains phenylalanine.

Zydis is a registered trademark of R.P. Scherer Corporation.

ZY 4036 103

17

Zyprexa Olanzapine

EXHIBIT 6
PAGE 17 OF 22

Methodology and study limitations

Study 1

A double-blind, randomized, placebo-controlled, 6-week study conducted at 23 sites in the US and Canada to compare the efficacy and safety of ZYPREXA 5.0±2.5, 10.0±2.5, and 15.0±2.5 mg/day with Haldol, 15.0±5.0 mg/day. The study involved 335 patients with a DSM-III-R diagnosis of schizophrenia.

Study 2

A double-blind, randomized, multicenter, international study to compare the efficacy and safety of ZYPREXA vs Risperdal. The study involved 339 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder, randomized to receive a dose range of 10-20 mg/day of ZYPREXA or 4-12 mg/day of Risperdal. Patients had the opportunity to complete 28 weeks of treatment; a total of 178 patients (52.5%) completed the study (ZYPREXA 57.6%; Risperdal 47.3%; P=.059).

- Patients treated with ZYPREXA initiated therapy at 15 mg/day for the first 7 days of treatment. Thereafter, investigators could adjust dose by 5 mg/day every 7 days (range 10-20 mg). The mean modal dose for ZYPREXA was 17.2 mg/day. Consistent with product labeling, patients treated with Risperdal began titration at a dose of 1 mg BID on day 1, 2 mg BID on day 2, and 3 mg BID on days 3 through 7. Thereafter, investigators could adjust dose by 2 mg/day every 7 days (range 4-12 mg/day). The mean modal dose for Risperdal was 7.2 mg/day.
- Treatment-emergent EPS was identified based on the following criteria: Simpson-Angus Scale total score >3 at any post-baseline visit for subjects with baseline ≤3; Barnes Akathisia Scale global score ≥2 at any post-baseline visit for subjects with baseline <2.
- Patients who were previously exposed to Risperdal were not excluded from this study, whereas patients previously exposed to ZYPREXA were.

Study 3

A double-blind, placebo-controlled, 4-week study conducted at 26 US sites to evaluate the efficacy and safety of ZYPREXA in the treatment of mania. Patients with a DSM-IV diagnosis of bipolar I disorder, manic or mixed, with or without psychotic symptoms, were randomized to receive a dose range of 5, 10, 15, or 20 mg/day of ZYPREXA or placebo for a 4-week period. Lorazepam use was permitted at 2 mg/day on days 1 to 4, 1 mg/day on days 5 to 10, and none thereafter. Starting dose of ZYPREXA was 15 mg/day. Patients had a baseline Young-Mania Rating Scale (Y-MRS) Total Score >20.

Study 4

A double-blind, placebo-controlled, 3-week study conducted at 8 US sites to evaluate the efficacy and safety of ZYPREXA in the treatment of mania. Patients with a DSM-IV diagnosis of bipolar I disorder, manic or mixed, with or without psychotic symptoms, were randomized to receive a dose range of 5, 10, 15, or 20 mg/day of olanzapine or placebo for a 3-week period. Lorazepam use was permitted at 4 mg/day on days 1 to 7, 2 mg/day on days 8 to 10, and none thereafter. Starting dose of ZYPREXA was 10 mg/day. Patients had a baseline Y-MRS Total Score >20.

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For additional safety profile and other important prescribing considerations, see pages 21-22 and the full Prescribing Information.
For safety information on Haldol, Risperdal, lorazepam, or Depakote, see manufacturer's package inserts.

Study 5

A double-blind, randomized, 3-week study conducted at 44 US sites to compare the efficacy and safety of ZYPREXA vs Depakote. The study involved 251 patients with a DSM-IV diagnosis of bipolar I disorder experiencing acute manic or mixed episodes (baseline Y-MRS total score >20), with or without psychotic features, with or without rapid cycling courses.

Dosing ranges were 5-20 mg/day for ZYPREXA and 500-2500 mg/day (divided doses) for Depakote, with starting doses at 15 mg QD for ZYPREXA and 750 mg BID or TID for Depakote. Mean ending doses were 17 mg QD for ZYPREXA and 1500 mg BID or TID for Depakote. Dosing adjustments could be made after 2 days and were based on clinical response and plasma levels. Plasma levels were measured to assess whether Depakote trough levels were maintained within the targeted therapeutic range of 50-125 µg/mL. Up to 4 blood samples were obtained per patient (mean, 2.7 samples); the mean value of all levels obtained was 79.4 µg/mL.

Study 6

A double-blind, randomized, placebo-controlled, 6-week study conducted at 12 sites to evaluate the efficacy and safety of ZYPREXA 1.0 and 10.0 mg/day. The study involved 152 patients with a DSM-III-R diagnosis of schizophrenia.

Study 7

Three independent studies were pooled to evaluate the treatment-emergent incidence of tardive dyskinesia (TD) in patients treated with double-blind, randomized, Haldol or ZYPREXA therapy for up to 2.6 years. A total of 1192 ZYPREXA-treated patients and 522 Haldol-treated patients with a DSM-III-R diagnosis of schizophrenia participated in one of three multicenter, double-blind, randomized studies. The first of these studies compared several dose ranges of ZYPREXA (5.0±2.5, 10.0±2.5, and 15.0±2.5 mg/day) with one dose range of Haldol (15.0±5.0 mg/day) and with placebo over six weeks. The second of these studies evaluated the same dose ranges of ZYPREXA and Haldol, but included a low dose of ZYPREXA (1.0 mg/day) in lieu of placebo. The third of these studies compared ZYPREXA (5.0 to 20.0 mg/day) with Haldol (5.0 to 20.0 mg/day) over six weeks. Patients responding to treatment in this study continued for up to 19 months thereafter, and ZYPREXA-treated patients completing the 19-month extension entered an open-label study.

- **HAMD-21 Total Score** is a 21-item observer-rated scale that assesses depressive symptoms. HAMD-21 individual items include: depressed mood, guilt, suicide, early insomnia, middle insomnia, late insomnia, work and activities, retardation, agitation, anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), genital symptoms, hypochondriasis, loss of weight (history), loss of weight (actual), insight, diurnal variation (present), diurnal variation (severity), depersonalization/derealization, paranoid symptoms, and obsessional/compulsive symptoms. Items are rated finely (on a 5-point scale) or coarsely (on a 3-point scale). Scores on the 5-point scale range from 1 (absent) to 5 (severe).

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- **Y-MRS Total Score** is an 11-item instrument used to assess the severity of mania. Depressive symptoms are not assessed. Y-MRS individual items include: elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech (rate and amount), language/thought disorder, thought content, disruptive/aggressive behavior, appearance, and insight. Items are rated on a 5-point scale, with varying descriptions for each.
- **PANSS Total Score** is a 30-item rating instrument that evaluates the positive, negative, and overall symptoms of schizophrenia. PANSS individual items include: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility, blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking, somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The items are rated on a 7-point scale from 1 (absent) to 7 (extreme).
- **SANS** obtains clinical ratings of negative symptoms in patients with schizophrenia across 5 subscales, including affective blunting, alogia, avolition/apathy, anhedonia/asociality, and disturbance of attention. The 24 total items in these subscales are each rated using a 6-point scale (0=not at all, 5=severe).
- **Simpson-Angus Scale for Parkinsonism:** The Extrapyramidal Side Effects Rating Scale, commonly referred to as the Simpson-Angus Scale, is a 10-item instrument used to measure drug-induced parkinsonism. Simpson-Angus individual items include: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor, and salivation. Items are rated on a 5-point scale from 0 (complete absence of the condition) to 4 (presence of the condition in extreme form).

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For additional safety profile and other important prescribing considerations, see the full Prescribing Information.
For safety information on Risperdal or Depakote, see manufacturers' package inserts.

Additional prescribing considerations

The most common treatment-emergent adverse event associated with ZYPREXA vs placebo in 6-week schizophrenia trials was somnolence (26% vs 15%). Also observed (ZYPREXA vs placebo) were:

postural hypotension (5% vs 2%)
akathisia (5% vs 1%)
constipation (9% vs 3%)
personality disorder* (8% vs 4%)
dizziness (11% vs 4%)
weight gain (6% vs 1%)

The most common treatment-emergent adverse event (reported in ≥10% of patients) with ZYPREXA vs risperidone in a schizophrenia trial was somnolence (26% vs 24%). Also observed (ZYPREXA vs risperidone) were:

anxiety (19% vs 17%)
insomnia (11% vs 14%)
nausea (4% vs 10%)
weight gain (16% vs 8%)
depression (6% vs 11%)
headache (15% vs 11%)
rhinitis (9% vs 14%)

The most common treatment-emergent adverse event associated with ZYPREXA vs placebo in short-term, placebo-controlled bipolar mania trials was somnolence† (35% vs 13%). Also observed (ZYPREXA vs placebo) were:

dry mouth† (22% vs 7%)
increased appetite (6% vs 3%)
constipation (11% vs 5%)
dyspepsia (11% vs 5%)
asthenia† (15% vs 6%)
dizziness† (18% vs 6%)
tremor (6% vs 3%)

Common and significantly different adverse events ($P<.01$) in a bipolar mania trial of ZYPREXA vs divalproex were:

somnolence (39.2% vs 20.6%)
nausea (10.4% vs 28.6%)
increased appetite (12.0% vs 2.4%)
dry mouth (33.6% vs 6.3%)

Other treatment-emergent adverse events reported in ≥5% of patients and significantly greater for ZYPREXA vs divalproex included tremor (9.6% vs 3.2%), neck rigidity (7.2% vs 1.6%), speech disorder (8.0% vs 0.8%), and sleep disorder (5.6% vs 0.8%).

Hemodynamic effects

In premarketing trials, some patients taking ZYPREXA experienced orthostatic hypotension associated with dizziness‡; tachycardia‡; and, in some cases, syncope (15/2500, 0.6%).

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* COSTART term for nonaggressive objectionable behavior.

† In bipolar mania trials, 4 adverse events occurred with statistically significantly higher significance with ZYPREXA than with placebo—none of these resulted in discontinuation.

‡ In acute-phase trials (n=356), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

Zyprexa
Olanzapine

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Transient, asymptomatic elevations of hepatic transaminase
In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients experienced jaundice or drug-induced hepatitis. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Effect on prolactin comparable to placebo
Modest elevations in prolactin were seen with ZYPREXA in acute-phase schizophrenia trials (incidence, 34% vs 13% with placebo). However, mean changes from baseline to endpoint were not statistically significantly different between ZYPREXA and placebo.

As with all antipsychotic medications, the following considerations should be taken into account when prescribing ZYPREXA:

Tardive dyskinesia (TD)—prescribing should be consistent with the need to minimize TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials of ZYPREXA (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Such conditions may be more prevalent in patients age 65 or older.

Use in patients with concomitant illness—in a clinical study involving nursing home patients having various psychiatric symptoms in association with Alzheimer's disease, somnolence, abnormal gait, fever, dehydration, and back pain were observed more often with ZYPREXA than with placebo. In two placebo-controlled studies in Parkinson's patients with drug-induced (dopamine agonist) psychosis, the following events occurred more often with ZYPREXA than with placebo: worsening of parkinsonian symptoms, hallucinations, somnolence, increased salivation, asthenia, and peripheral edema. As with other CNS-active drugs, ZYPREXA should be used with caution in elderly patients with dementia and/or Parkinson's disease.

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For additional safety profile and other important prescribing considerations, see the full Prescribing Information.

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