

ZYPREXA IMPLEMENTATION GUIDE

For your information **ONLY**; not for use in detailing.

TABLE OF CONTENTS

1. Strategy Overview
 2. Message Flow
 3. Objection Handling
 4. Frequently Asked Questions
 5. Competitive Grid
-

STRATEGY OVERVIEW

Welcome to the Primary Care Resource Guide. This guide will function as your resource for our launch of the Primary Care message. Our vision is to expand the market of ZYPREXA by redefining how primary care physicians help reduce mood, thought, and behavioral disturbances. Our strategy is to establish the position of ZYPREXA as a “safe, proven solution for mood, thought, and behavioral disturbances related to schizophrenia and bipolar mania.” We can accomplish this by:

- Placing a strong emphasis on direct-to-physician marketing; establishing ZYPREXA as the next incremental step in the PCP’s treatment and prescription orbit
- Broadly targeting office-based PCPs
- Communicating a message based on patients’ symptoms and behaviors

Symptoms and behaviors...

In order to succeed in the Primary Care market, we must focus on the *symptoms and behaviors* found in mood, thought, and behavioral disturbances. The sales aid has been organized in such a fashion that will allow you to identify specific symptoms for these disturbances. This message flow and the patient profiles (Martha, David, and Christine) will aid you in helping the physician to recognize these symptoms in patients he or she sees frequently. Use these tools to aim for early identification of relevant patient types, as well as pointing out the important role that the family members play.

Proven safety...

Because many primary care physicians may not be familiar with the safety profiles of the newer psychotropic medications, we must emphasize the safety of ZYPREXA and its low risk of certain serious medical complications, safety that is proven by 5 years of use and over 5 million patients treated.

FRMR SLS REP 00113

Effectiveness...

When communicating our message, be sure to define effectiveness as the following:

“Effectiveness”: efficacy + ease of use + well tolerated = compliance

As we know, compliance can be an issue for some patients. Be sure to point out that ZYPREXA is effective in treating symptoms, but its ease of use (QD dosing with or without food, no blood monitoring) and its generally safe profile may allow for a higher compliance rate.

Key message elements...

In essence, the ZYPREXA Primary Care message has a “3X3” component to it. The three sets of disturbances we need to focus on are:

- Mood disturbances
- Thought disturbances
- Behavioral disturbances

We then have three components to our message:

- Broad efficacy (refer to 3 patient types: Martha, David, Christine)
- Safety (Proven: 5 years, 5 million patients, low risk of certain serious medical complications)
- Ease of use (5 mg to start, QD, at bedtime, with or without food, no blood monitoring)

In closing, we hope you will find this information helpful for the new challenge you are taking on. As a Primary Care representative, you need to have the flexibility to handle both situational and sit down messages. We appreciate your dedication and expertise and are counting on these attributes as we launch into the market of Primary Care!

ZYPREXA - PRIMARY CARE MESSAGE FLOW

Cover

Objective:

- Assure physicians that they can effectively treat the symptoms associated with various mental disorders frequently observed in patients that physicians know and treat.
- Introduce ZYPREXA, a versatile agent that will allow physicians to treat these patients more effectively.

Key message:

ZYPREXA is a safe psychotropic with proven efficacy in treating mental illness and reducing symptoms of mood, thought, and behavioral disturbances.

Sales Call:

Doctor, you know your patients better than any other clinician. Your patients rely on you to help them manage their mental health, and some may present with one or more of the following symptoms: agitation, elevated mood, aggressiveness, disorientation, and suspiciousness. What happens when they don't respond to "ordinary" treatment? Referrals can be expensive, difficult to schedule, or rejected by the patient.

I would like to share information with you about ZYPREXA, a versatile psychotropic agent indicated for bipolar mania and schizophrenia that may help these patients and their families. Let's meet one of these patients.

(Patient profile #1):

Martha is a widow you've known and treated for several years. As she's aged, she's become more complicated to manage—clinically, and at home. These are comments you hear from her family (read testimonials from profile). Your main goal of treatment is to treat her illness and reduce her behavioral disturbances. Do you see patients like Martha?

(Patient profile #2):

David is highly functional, and in good general physical health. He's been a patient of yours for a few years, and has been having trouble lately. His history includes treatment with several different antidepressants, but his current symptoms are not being well controlled. This is how David's wife describes him (read testimonials from profile). Your main goal of treatment is to treat and stabilize his mood disorder. Do you see patients like David?

(Patient profile #3):

Christine is in her 20s, single, and has a history of poor work performance. You've ruled out substance abuse, yet she continues to struggle. These are comments you hear from her family (read testimonials from profile). Your main goal of treatment is to treat her thought disturbances. Do you see patients like Christine?

Back cover

Sales Call:

Doctor, ZYPREXA is a psychotropic agent proven to be effective in treating symptoms found in behavior, mood, and thought disorders. No other single agent offers this broad spectrum of efficacy. Yet, ZYPREXA is generally safe and is easy to use.

Doctor, when I say "proven," I am referring to ZYPREXA being on the market for 5 years with more than 5 million patients treated. And as you can see, ZYPREXA is safe for a patient like (patient): (read bullet points).

As you know, compliance is crucial—the agent you choose must be well tolerated, effective, and easy to use. With ZYPREXA, you get all three, including once-daily dosing without regard to meals. We recommend that you start at 5 mg and make adjustments depending on your clinical judgment. With your permission, Doctor, I'd like to share more of the ZYPREXA story with you, including other patients who could benefit from this unique agent. Would now be a good time to do that?

Inside front cover

(Optional spread, appropriate for the amiable, conversational customer.)

Objective:

- Reassure the PCP that ZYPREXA is a "proven" product for the treatment of multiple mental disorders.
- Highlight both indications (schizophrenia and bipolar mania) to the PCP.
- Reinforce the efficacy ZYPREXA offers for mood, thought, and behavioral disturbances.

Key Message:

ZYPREXA is a versatile psychotropic proven effective in a large number of patients who suffer from mood, thought, and behavioral disturbances.

Sales Call:

ZYPREXA may be somewhat new to you, but it is already well established among psychiatrists. ZYPREXA launched as an antipsychotic in 1996 for the management of the manifestations of psychotic disorders associated with schizophrenia. But the proven efficacy of ZYPREXA doesn't stop there; it received approval in March 2000 for the treatment of acute bipolar mania. In 4 years, ZYPREXA has been prescribed for more

than 5 million people. We believe that the unique combination of broad efficacy, safety, and ease of use of ZYPREXA will meet your needs as a primary care physician.

Page 1

Objective:

- Educate the PCP about the outstanding efficacy profile of ZYPREXA in treating the disorder and controlling the symptoms and behaviors of mental illness.
- Reassure
- the PCP with information about the outstanding safety profile of ZYPREXA.
- Emphasize the simple once-daily dosing regimen of ZYPREXA.

Key Message:

ZYPREXA is proven effective in treating the illness and controlling the symptoms and behaviors of mental disorders with a low potential of treatment-emergent adverse events such as EPS or QTc prolongation. ZYPREXA is also easy to use with its once-daily dosing regimen and no need for blood monitoring.

Sales Call:

Here are some likely questions you, your patients, or their families may have about ZYPREXA (read questions).

Pages 2-3

Objective:

- Emphasize that ZYPREXA is effective in treating the disorder and controlling the symptoms and behaviors associated with mental illness, including the troubling behavioral symptoms that can result in disruptive actions and caregiver burdens.
- Point out that ZYPREXA begins to control behavioral symptoms as early as week 1.
- Emphasize improvement (reduction) in hostility in patients taking ZYPREXA.
- Frame BPRS as a commonly used psychiatric scale, and point out that the reduction in hostility is significant (refer to the BPRS tear sheet, review key symptoms).

Key Message:

ZYPREXA effectively treats the illness and reduces the symptoms associated with behavioral disturbances as early as week one. ZYPREXA effectively reduces the troublesome behavioral symptom of hostility.

Sales Call:

Behavioral disturbances wreak havoc at home and in your waiting room. This graph demonstrates how ZYPREXA works to improve overall symptoms by reducing hostility, tension, uncooperativeness and agitation. What agents do you currently turn to for help with these symptoms? ZYPREXA offers relief from these symptoms as early as week 1, and continues to improve through week 6.

(Page 3) This graph shows an 18% reduction in hostility, as measured by a common psychiatric scale. This level of improvement is significant; reducing hostility enhances overall patient care—it also may increase compliance and decrease caregiver burden. And, it also may result in fewer phone calls to your office.

Pages 4-5**Objective:**

- Demonstrate that anxious and depressive symptoms were significantly reduced in patients treated with ZYPREXA.
- Reinforce the point that ZYPREXA effectively improves symptoms associated with depressed mood including social withdrawal, apathy, and flat affect.
- Communicate that manic symptoms were also significantly reduced in patients treated with ZYPREXA.

Key message:

- ZYPREXA is an effective treatment for anxious, depressive, and manic symptoms associated with mood disturbances. In addition to effectively treating symptoms of anxiety and depression, ZYPREXA works to improve other significant emotional symptoms including social withdrawal, apathy, and flat affect. ZYPREXA also improves manic symptoms, such as elevated mood, increased activity/energy, disturbed sleep, irritability, and language/thought disorder.

Sales Call:

ZYPREXA can also improve depressive symptoms.

Your patients with mood disturbances may present with symptoms of social withdrawal, apathy and flat affect. Psychiatrists refer to these as "negative symptoms," but (patient's)

family may say it more simply: "She's just not herself anymore." ZYPREXA improves these symptoms. With ZYPREXA, (patient) may become more socially involved, and interact more with family and loved ones.

In our bipolar mania disorder clinical trials, ZYPREXA significantly improved symptoms of bipolar mania. These symptoms include elevated mood, sleep disturbance and disruptive behavior. Do you see patients with these symptoms?

Page 6

Objective:

- Point out that ZYPREXA does not impair cognition.
- Emphasize that ZYPREXA may, in fact, improve certain cognitive items, such as organized thinking, attention, and judgment and insight.

Key Message:

ZYPREXA does not impair cognition, and may even improve certain cognitive items such as organized thinking, attention, and judgment and insight.

Sales Call:

Cognition, the ability to think clearly, is very important to patients and their families. ZYPREXA does not impair cognition; in fact, ZYPREXA has been shown to improve cognition, including specific items such as organized thinking, attention, and judgment and insight. Thought disturbances, which impact cognition, are common psychotic symptoms and may be co-morbid with other conditions. Would you agree that ZYPREXA can help these patients?

Page 8

Objective:

- Highlight that there was no statistically significant difference between ZYPREXA and placebo in EPS rating scores.

Key Message:

There was no significant difference in EPS rating scores between ZYPREXA and placebo across the dosage range.

Sales Call:

The proven efficacy of ZYPREXA in behavior, mood, and thought disturbances is established in clinical trials. For primary care physicians and their patients, it's absolutely critical that an agent be safe, so let's review the safety profile of ZYPREXA. Because ZYPREXA was initially approved as an antipsychotic, it is important that you know what to expect with regard to treatment-emergent extrapyramidal symptoms (EPS). The good news for you and your patients is that the EPS profile of ZYPREXA is comparable to placebo across the dosage range. Other agents, such as Haldol or Risperdal, have been associated with dose related EPS, especially as the dose is increased.

Page 9

Objective:

- Point out the ease of use of ZYPREXA—once-daily dosing, with or without food, and no blood monitoring is required.

Key Message:

ZYPREXA is easy to use.

Sales Call:

As noted, ZYPREXA offers ease of use: once-daily dosing, with or without food, any time of day. We recommend a starting dose of 5 mg at bedtime or 2.5 mg in special populations. In short, think of ZYPREXA as "safe" and "easy to use." It's a good fit with primary care.

Page 10

Objective:

- Emphasize the low risk of certain serious medical complications with ZYPREXA.
- Point out that ZYPREXA has a low potential for drug-drug interactions.
- Highlight the ability of ZYPREXA to fit in with patient's daily routines (no blood monitoring required, little, if any effect on prolactin).

Key message:

ZYPREXA has a low risk for certain serious medical complications, and is compatible with patient's daily routines.

Sales Call:

This list outlines the low risk for certain serious medical complications with ZYPREXA. Let's start with drug interactions: there is very little potential for P450 inhibition, meaning that the interaction risk for ZYPREXA is very low. So, for your patients who are taking other medications such as warfarin, you can safely add ZYPREXA.

Since adverse cardiac events can be a concern, it is good to know that there is no need for a baseline ECG with ZYPREXA, which is required for some psychotropics that cause QTc prolongation. Doctor, isn't it good to know that there was no difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials?

Another advantage of ZYPREXA is that there is no need for blood monitoring, unlike some mood stabilizers such as lithium. Not only does this speak to the safety of ZYPREXA, but this makes treatment with ZYPREXA that much more convenient for both you, your patients, and their families.

Doctor, I'd like to point out that there are no black box warnings for ZYPREXA, unlike Depakote, a mood stabilizer that has 3 black box warnings for hepatotoxicity, teratogenicity, and pancreatitis. As you may or may not know, the FDA requires a prominently displayed boxed warning on a product's label for special problems that may lead to death or serious injury.

Another good point about ZYPREXA is that the reporting rate for constipation among patients was not statistically different from placebo-treated patients. ZYPREXA may be a good alternative for patients who are at risk for anticholinergic side effects such as this.

Doctor, patient non-compliance is one of the major causes of relapse of symptoms. Certain troublesome side effects can result in patient non-compliance, especially those that may cause sexual dysfunction. You and your patients won't have to worry about such side effects with ZYPREXA, since its effect on prolactin is comparable to placebo. I think you will agree that ZYPREXA offers a safe choice for your patients. Are any of these safety issues of great concern to you? How does ZYPREXA compare to other agents you may have considered?

Page 11

Objective:

- Point out that the discontinuation rate due to adverse events is comparable to placebo.
- Emphasize the safety and tolerability of ZYPREXA.

Key message:

ZYPREXA is safe and tolerable. The most common treatment-emergent side effect is somnolence.

Sales Call:

The proven tolerability of ZYPREXA is captured here: the discontinuation rate due to adverse events is comparable to placebo. ZYPREXA, like all drugs, has the potential to cause side effects. Somnolence was the most common, others are listed here (read list of adverse events). As with many agents in its class, ZYPREXA is sometimes associated with weight gain. For most patients, this is very manageable. Again, the discontinuation rate due to adverse events is comparable to placebo.

One of the reasons ZYPREXA has been so popular with psychiatrists is its risk/benefit profile. ZYPREXA is generally safe, easy to use, and provides you, the primary care physician, with broad efficacy. Would you agree with that statement, based on what we've reviewed?

Well, doctor, the next step is simple: gaining clinical experience with ZYPREXA. Consider the proven efficacy, safety, and ease of use of ZYPREXA for your patients like (patient) whose symptoms of behavior, mood, and thought warrant a solution. A solution like ZYPREXA. Can you think of patients in your practice right now who might benefit from ZYPREXA?

OBJECTION WORKSHOP

1. I have heard that ZYPREXA causes weight gain.

PROBE: Has that been your clinical experience?

RESPONSE: ZYPREXA, like many psychotropic agents, is associated with weight change. The majority of patients taking Zyprexa experienced modest or no weight gain. It is important to note that weight gain, when it occurred, stabilized over time. More specifically, mean weight change plateaued after the first 39 weeks of treatment. In a 28-week head-to-head trial with risperidone, the average weight gain with ZYPREXA was 9 lb vs 5 lb for risperidone.

2. I do not treat schizophrenia or bipolar disorder.

PROBE: Doctor, would you agree that you see patients who present with symptoms of mood, thought, and behavioral disorders who are not responding to your satisfaction?

For those patients you identify for a psych referral, do you find that there can be delays, insurance coverage issues, or simply patient refusal?

How do you approach these patients?

(Bridge into selling at this point.)

3. I am concerned that my patients may develop EPS/TD.

Doctor, that is understandable. Have you had any of your own patients experience some of these unfortunate side effects? On what agents? Unlike other psychotropic agents, the good news is that across all dosage ranges the incidence of EPS for ZYPREXA is comparable to placebo.

In fact, in clinical trials the incidence of TD with haloperidol is 12 times greater than with ZYPREXA (0.5%), which is equal to placebo.

I can send you a medical letter.

FREQUENTLY ASKED QUESTIONS

How do I switch from other psychotropics to ZYPREXA?

Add ZYPREXA and slowly taper off the other psychotropic based on your clinical judgment. I can send a medical letter.

This is a great opportunity for you to attend a peer-to-peer program and discuss this further with your peers.

What about the cost?

At the dosage range of 2.5 to 5 mg, the NWP of ZYPREXA is \$4-\$5 per day.

With all the benefits that ZYPREXA offers your patients, all we ask is that you talk with your patients about it and let them make the choice.

How does Zyprexa compare with Haldol?

Is there some specific aspect you would like to explore?

In a head-to-head trial of nearly 2,000 patients, ZYPREXA was numerically superior to haloperidol in positive symptoms and statistically superior in negative symptoms, depressive symptoms, side effects (including EPS and prolactin), and discontinuation due to adverse events.

I can supply you with a medical letter on this study.

Do I need to do any blood monitoring with ZYPREXA?

No.

I have heard that ZYPREXA causes diabetes.

Has this been your clinical experience?

In a large (n=5,022) retrospective analysis, the incidence of treatment-emergent glucose elevations with ZYPREXA was comparable to placebo (3.1% vs 2.5%). Further, the incidence of developing diabetes while on ZYPREXA is not statistically different from the population at large.

I can supply you with a medical letter that can provide further details.

Does ZYPREXA cause anticholinergic side effects?

Has this been your clinical experience?

ZYPREXA is a pharmacologically rich molecule and it does affect several receptors. Interestingly, the in vitro profile of ZYPREXA does not correlate to side effects seen in our clinical trials. Discontinuation rates due to adverse events, including dry mouth, constipation, and blurred vision, are comparable to placebo.

Does ZYPREXA cause prolactin elevations?

In the clinical trials of ZYPREXA, some patients experienced a slight increase in prolactin levels. However, this elevation did not differ from placebo, unlike haloperidol and risperidone.

With ZYPREXA, your patients do not need to worry about embarrassing side effects such as galactorrhea, gynecomastia, amenorrhea, and sexual dysfunction; or long-term effects of prolactin elevation such as osteoporosis or breast cancer.

Does ZYPREXA cause QTc prolongation?

With the recent mailing of Mellaril/Serentil warning letters (black box warnings) to all primary care physicians regarding QTc safety, and the withdrawal of medications such as Seldane, Hismanal, and Propulsid, the awareness of cardiac safety has been raised quite significantly. With ZYPREXA, there is no baseline ECG required; in fact, there was no difference in clinically significant QTc prolongation compared to placebo.

I've heard that ZYPREXA causes a lot of somnolence?

In schizophrenia clinical trials, 26% of patients treated with ZYPREXA experienced somnolence vs 13% on placebo. According to the package insert, this

side effect is dose-dependent (lower doses have less sedation and tends to be transient). Also, several opinion leaders describe this calming effect as a therapeutic benefit and choose to dose it at bedtime.

Competitive Review

Product	Negative Features (our verbatim)	Positioning (not our verbatim)	What this means to Martha, David, and Christine
Risperdal	<ul style="list-style-type: none"> * Dose dep. EPS/TD * Prolactin elevations * Risk of orthostasis 	<ul style="list-style-type: none"> * Resembles Haldol, risks outweigh benefits 	<ul style="list-style-type: none"> * More adverse events than Zyprexa with less efficacy * MD is forced to titrate to side effects as opposed to titrating to therapeutic effect * Refer to Tran study
Haldol	<ul style="list-style-type: none"> * EPS/TD liability * Efficacy limited to positive symptoms * BID-TID * Drug interactions 	<ul style="list-style-type: none"> * High risk (EPS/TD) with limited benefit 	<ul style="list-style-type: none"> * High risk for serious irreversible side effects and does not address negative symptoms, depression or cognition
Seroquel	<ul style="list-style-type: none"> * Sedation * Falls * Cataracts (in animals) * Complicated dosing 	<ul style="list-style-type: none"> * Overtly sedating, difficult to dose and could lead to falls 	<ul style="list-style-type: none"> * Low compliance due to sedation, and for Martha a fall could lead to serious complications or could accelerate progression to a nursing home
Ziprasidone	<ul style="list-style-type: none"> * Cardiac safety concern * Unproven * BID * Dose dep. EPS * Disappointing response rates 	<ul style="list-style-type: none"> * Unproven agent that carries the risk of sudden death-not a primary care agent 	<ul style="list-style-type: none"> * Cardiac safety concerns-QTc is too risky * High risk-limits benefits
Depakote	<ul style="list-style-type: none"> * Multiple black box warnings * Requires blood monitoring 	<ul style="list-style-type: none"> * Not a primary care agent; liability laden 	<ul style="list-style-type: none"> * Risk for pancreatitis, hepatotoxicity, or teratogenicity Frequent trips to the office for unpleasant blood draws
Mellaril	<ul style="list-style-type: none"> * QTc prolongation-Black box * Limited efficacy * Highly anticholinergic 	<ul style="list-style-type: none"> * Outdated choice with cardiac risk 	<ul style="list-style-type: none"> * High risk for cardiac problems-does not address negative symptoms, depression, or cognition.
Lithium	<ul style="list-style-type: none"> * Highly toxic * Impairs cognition * BID-TID * Cardiac, thyroid, and renal concerns 	<ul style="list-style-type: none"> * Outdated choice with toxicity, organ concerns 	<ul style="list-style-type: none"> * Does not treat psychosis * Frequent trips to office for blood tests * A risky choice
<u>Antidepressants</u>	<ul style="list-style-type: none"> * Can induce mania * Does not treat psychosis * Frequently ineffective for agitation 	<p style="text-align: center;">Companion Classes (Drugs that Zyprexa may augment-not replace)</p>	<p style="text-align: center;">Cholinesterase Inhibitors</p> <ul style="list-style-type: none"> * Ineffective for psychosis * Limited, delayed utility-slow onset * Ineffective for mood disorders
	<p style="text-align: center;">Limitations</p>	<p style="text-align: center;">Limitations</p>	<p style="text-align: center;">Limitations</p>