PRODUCT INFORMATION

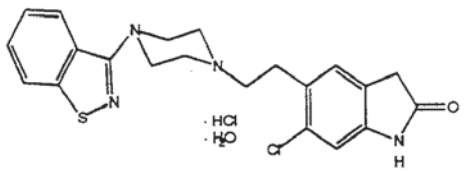
ZELDOX® (ziprasidone hydrochloride)

NAME OF THE MEDICINE

The chemical name for ziprasidone hydrochloride is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, monohydrochloride monohydrate.

Australian Approved Names: Ziprasidone ($C_{21}H_{21}ClN_4OS$) and Ziprasidone hydrochloride ($C_{21}H_{21}ClN_4OS.HCl.H_2O$).

The structural formula of ziprasidone hydrochloride is shown below:



The molecular formula of ziprasidone hydrochloride is $C_{21}H_{21}ClN_4OS.HCl.H_2O$. Ziprasidone hydrochloride has a molecular weight of 467.42 and the free base has a molecular weight of 412.94.

The CAS Registry Numbers are 146939-27-7 (ziprasidone) and 138982-67-9 (ziprasidone hydrochloride).

DESCRIPTION

Ziprasidone is an antipsychotic agent for oral administration. It is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents.

Ziprasidone is a white to slightly pink powder. The measured solubility of ziprasidone hydrochloride is 0.0075% w/v in water at 37°C and 0.0041% w/v in a pH 3.0 buffer at 25°C.

ZELDOX is supplied for oral administration as capsules containing ziprasidone hydrochloride monohydrate equivalent to 20 mg, 40 mg, 60 mg and 80 mg ziprasidone, and contains the following inactive ingredients: lactose, starch-pregelatinised maize, magnesium stearate, gelatin, titanium dioxide and indigo carmine CI73015 (20 mg, 40 mg and 80 mg capsules only), TekPrint SW-9008 Black Ink.

PHARMACOLOGY

Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$ and $5HT_{1D}$ and α_1-adrenergic receptors (K_is of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively) and moderate affinity for the histamine H_1 receptor (K_i=47 nM).

Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A,}$ and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and noradrenaline. No appreciable affinity was exhibited for the other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50}>1μM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Positron Emission Tomography Studies

At 12 hours following a 40 mg dose of ziprasidone, receptor blockade was greater than 80% for $5HT_{2A}$ and greater than 50% for D_2 using positron emission tomography (PET).

Pharmacokinetics

Absorption

Following oral administration of multiple doses of ziprasidone with food, peak serum concentrations typically occur 6 to 8 hours post-dose. Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 40-80 mg twice daily in fed subjects. The absolute bioavailability of a 20 mg dose is 60% in the fed state.

Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is significantly increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food.

Distribution

Ziprasidone is greater than 99% protein bound, binding primarily to albumin and α_1-acid glycoprotein. Twice daily dosing generally leads to attainment of steady state within one to three days. Systemic exposures at steady state are related to dose. Ziprasidone has a volume of distribution of approximately 1.1 L/kg when administered intravenously.

Metabolism

Ziprasidone is extensively metabolised after oral administration with only a small amount excreted in the urine (<1%) or faeces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the faeces. Unchanged ziprasidone represents about 44% of total drug-related concentration in serum.

In vitro studies indicate that CYP3A4 is the major cytochrome catalysing the oxidative metabolism of ziprasidone with some potential contribution from CYP1A2.

S-methyl-dihydroziprasidone is generated in two steps catalysed by aldehyde oxidase and thiol methyltransferase.

Ziprasidone, S-methyl-dihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QTc-prolonging effect. S-methyl-dihydroziprasidone is mainly eliminated by biliary excretion and CYP3A4 catalysed metabolism. The sulphoxide is eliminated through renal excretion and by secondary metabolism catalysed by CYP3A4 (see **INTERACTIONS WITH OTHER MEDICINES**).

Excretion

The mean terminal phase half-life after multiple dosing in normal volunteers and schizophrenic patients is between 6 and 10 hours, with a range of individual values from 3 to 18 hours.

Mean systemic clearance of ziprasidone administered intravenously is approximately 5 mL/min/kg.

Special Populations

Elderly (>65 years)

There are no clinically significant differences in the pharmacokinetics of ziprasidone in young adults and elderly.

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between elderly (>65 years) and young (18 to 45 years) adult subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age are, therefore, not recommended.

Children and Adolescents

Ziprasidone has not been systematically evaluated in subjects under 18 years of age.

Gender

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for gender are, therefore, not recommended.

Race

No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking

Based on *in vitro* studies utilising human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

Renal Impairment

Because ziprasidone is highly metabolised, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg twice daily dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by haemodialysis.

No marked differences in the pharmacokinetics of ziprasidone have been observed in patients with decreased kidney function (creatinine clearance >10 mL/min).

Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Child Pugh Class A and B) cirrhosis revealed an increase in AUC_{0-12} of 13% and 34% in Child Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

CLINICAL TRIALS

Schizophrenia

The efficacy of ziprasidone in the management of the manifestations of psychotic disorders was established in three short-term (4- and 6-week) and one long-term (52 week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia or schizoaffective disorder. Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS), both multi-item inventories of psychopathology traditionally used to evaluate the effects of drug treatment in psychosis.

Another traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for the Assessment of Negative Symptoms (SANS) and the Montgomery-Asberg Depression Rating Scale (MADRS) were employed in some clinical trials.

In the 52-week, placebo-controlled maintenance trial (N=294), ziprasidone doses of 20, 40 and 80 mg twice daily were statistically superior to placebo in the prevention of recurrent exacerbation of the illness, as well as in the BPRS total and psychosis cluster, the CGI, the

PANSS total and negative subscale, and Global Assessment of Functioning. Discontinuations due to adverse events were 7-10% in the ziprasidone groups and 15% in the placebo group.

An analysis of the effect of ziprasidone on patients with clinically significant depressive symptoms (MADRS) ≥14 was conducted in two multicentre placebo-controlled studies in acute schizophrenia. A statistically significant improvement versus placebo ($p<0.05$) in the MADRS was observed in patients receiving ziprasidone 60 mg twice daily in one study and 80 mg twice daily in another study.

Bipolar Mania

The efficacy of ziprasidone in mania was established in two placebo-controlled, double-blind, 3-week studies which compared ziprasidone with placebo and one double-blind, 12-week study, which compared ziprasidone to haloperidol and placebo. These studies included 850 patients meeting DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features. Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behaviour and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression – Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

In a 3-week placebo-controlled, double-blind trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score ($p\leq0.01$).

In a second 3-week placebo-controlled, double blind trial (n=205), the dose of ziprasidone was 40 mg twice daily on Day 1. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score ($p\leq0.01$ and $p\leq0.001$ respectively).

In the 12-week placebo-controlled, double-blind, double-dummy trial (n=437), patients were randomised to ziprasidone, haloperidol, or placebo in a ratio of 2:2:1. Patients randomised to ziprasidone or haloperidol took their assigned drug for the 12-week study period. Patients randomised to placebo took placebo for the first 3 weeks of treatment and were then switched to ziprasidone for the remaining 9 weeks of the study. During the first 3 weeks of randomised study medication, the dose of ziprasidone was within the range of 40-80 mg twice daily and the dose of haloperidol was within the range of 4-15 mg twice daily. During the last 9 weeks of treatment, drug dosages could be reduced to as low as 20 mg twice daily for ziprasidone and 2 mg twice daily for haloperidol. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score ($p<0.001$) and CGI-S score ($p=0.002$) at Week 3. In ziprasidone treated patients, significant treatment differences were shown in MRS total score at Day 2 ($p=0.001$) and maintained at Day 7 ($p=0.016$) and Day 14 ($p=0.001$) and in CGI-S scores starting at Day 14 ($p<0.001$). Haloperidol was also

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.