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ALTERNATE SYNTHETIC APPROACHES TO ZIPRASIDONE, PREPARATION AND CHARACTERIZATION OF ITS RELATED COMPOUNDS

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Alternate Synthetic Approaches to Ziprasidone, Preparation and Characterization of Its Related Compounds

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Abstract:- A series of substituted piperazine derivatives have been synthesized and tested for antibacterial activity. The antibacterial activity was tested against Gram-positive and Gram-negative bacteria strains like B. subtilis, B. pumillis, E. coli, and P. aeruginosa. These entire compounds have been characterized by their IR and 1H NMR spectral data. All synthesized compounds showed significant activity against bacterial strains. The biological screening showed that the compounds Vc, Vd and Ve are the most active ones showing an interesting antibacterial activity.

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1.1 INTRODUCTION

Ziprasidone (marketed as Geodon, Zeldox by Pfizer) was the fifth atypical antipsychotic to gain approval (February 2001) in the United States. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia, and acute mania and mixed states associated with bipolar disorder. Its intramuscular injection form is approved for acute agitation in schizophrenic patients for whom treatment with just ziprasidone is appropriate.

Ziprasidone is also used off-label for depression, bipolar maintenance, mood disorders, anxiety, aggression, dementia, attention deficit hyperactivity disorder, obsessive compulsive disorder, autism, and post-traumatic stress disorder.

The oral form of ziprasidone is the hydrochloride salt, ziprasidone hydrochloride. The intramuscular form, on the other hand, is the mesylate salt, ziprasidone mesylate trihydrate, and is provided as a lyophilized powder.

Ziprasidone's affinities for most of the dopamine and serotonin receptors and the α1-adrenergic receptor are high and its affinity for the histamine H1 receptor is moderate. It also displays some inhibition of synaptic reuptake of serotonin and norepinephrine, though not dopamine.

Ziprasidone's efficacy in treating the positive symptoms of schizophrenia is believed to be mediated primarily via antagonism of the dopamine receptors, specifically D2. Blockade of the 5-HT2A receptor may also play a role in its effectiveness against positive symptoms, though the significance of this property in antipsychotic drugs is still debated among researchers. Blockade of 5-HT2A and 5-HT2C and activation of 5-HT1A as well as inhibition of the reuptake of serotonin and norepinephrine may all contribute to its ability to alleviate negative symptoms. The relatively weak antagonistic actions of ziprasidone on the α1-adrenergic and H1 receptors likely in part explain some of its side effects, such as sedation and orthostatic hypotension. Unlike many other antipsychotics, ziprasidone has no significant affinity for the mACh receptors, and as such lacks any anticholinergic side effects.

The systemic bioavailability of ziprasidone is 100% when administered intramuscularly and 60% when administered orally with food. After a single dose intramuscular administration, the peak serum concentration typically occurs at about 60 minutes after the dose is administered, or earlier. Steady state plasma concentrations are achieved within one to three days. The mean half-life ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Ziprasidone absorption is optimally achieved when administered with food. Without a meal preceding dose, the bioavailability of the drug is reduced by approximately 50%.

Ziprasidone is hepatically metabolized by aldehyde oxidase; minor metabolism occurs via cytochrome P450 3A4 (CYP3A4). Medications that induce (e.g. carbamazepine) or inhibit (e.g. ketoconazole) CYP3A4 have been shown to decrease and increase, respectively, blood levels of ziprasidone.

Ziprasidone received a black box warning due to increased mortality in elderly patients with dementia-

related psychosis. It also slightly increases the QTc interval in some patients and increases the risk of a potentially lethal type of heart arrhythmia known as torsades de pointes. Ziprasidone should be used cautiously in patients taking other medications likely to interact with ziprasidone or increase the QTc interval.

Ziprasidone is known to cause activation into mania in some bipolar patients. This medication can cause birth defects, according to animal studies, although this side effect has not been confirmed in humans.

Adverse events reported for ziprasidone include severe chest pains, impaired erectile function and stimulation, sedation, insomnia, orthostatic hypotension, life-threatening neuroleptic malignant syndrome, akathisia, and the development of permanent neurological disorder tardive dyskinesia. Rarely, temporary speech disorders may result.

Recently, the FDA required the manufacturers of some atypical antipsychotics to include a warning about the risk of hyperglycemia and Type II diabetes with atypical antipsychotics. Some evidence suggests that ziprasidone may not be as bad as some of the other atypical antipsychotics (namely, olanzapine (Zyprexa)) at causing insulin resistance and weight gain. In fact, in a trial of long term therapy with ziprasidone, overweight patients (BMI > 27) actually had a mean weight loss overall; however, a common side-affect of the drug is nausea and anorexia. According to the manufacturer insert, ziprasidone caused an average weight gain of 2.2 kg (4.8 lbs) (which is significantly lower than other atypicals–clozapine and olanzapine).

Ziprasidone should be discontinued gradually, with careful consideration from the prescribing doctor, to avoid withdrawal symptoms or relapse. Withdrawal may become even more difficult after failed attempts. [citation needed]

The British National Formulary recommends a gradual withdrawal when discontinuing anti-psychotic treatment to avoid acute withdrawal syndrome or rapid relapse. Due to compensatory changes at dopamine, serotonin, adrenergic and histamine receptor sites in the central nervous system, withdrawal symptoms can occur during abrupt or over-rapid reduction in dosage.

Support groups such as The Icarus Project and other online forums provide resources and social support for those attempting to discontinue antipsychotics and other psychiatric medications. Withdrawal symptoms reported to occur after discontinuation of antipsychotics include nausea, emesis, lightheadedness, diaphoresis, dyskinesia, orthostatic hypotension, tachycardia, nervousness, dizziness, headache, excessive non-stop crying, and anxiety. Some have argued that additional somatic and psychiatric symptoms associated with dopaminergic super-sensitivity, including dyskinesia and acute psychosis, are common features of withdrawal in individuals treated with neuroleptics. This has led some to suggest that the withdrawal process might itself be schizo-mimetic, producing schizophrenia-like symptoms even in previously healthy patients, indicating a possible pharmacological origin of mental illness in a yet unknown percentage of patients currently and previously treated with antipsychotics. This question is unresolved, and remains a highly controversial issue among professionals in the medical and mental health communities, as well the public. Complicated and long-lasting rebound insomnia symptoms can also occur after withdrawing from antipsychotics.

1.2 ZIPRASIDONE BINDING PROPERTIES

The second-generation antipsychotic (SGA), ziprasidone, has proven efficacy in the treatment of schizophrenia and mania. Ziprasidone combines an antipsychotic efficacy similar to that of the prototypic first- eneration antipsychotic (FGA), haloperidol, with the advantages of moderate extrapyramidal and minimal occurrence of sexual, vegetative, and metabolic side effects. Ziprasidone is a D_2/D_3 dopamine and 5-HT_2 serotonin-receptor antagonist of relatively high affinity. In addition, it is a partial 5-HT_{1A}–receptor agonist and a serotonin and noradrenaline transporter reuptake inhibitor.

Previous positron emission tomography (PET) or single-photon emission computed tomography investigations revealed 60% to 75% striatal D_2/D_3-receptor occupancy in patients obtaining clinically effective doses/plasma concentrations.

However, the extent of ziprasidone binding to extrastriatal D2/D3 dopamine receptors has not yet been determined.

With the advent of high-affinity radiotracers belonging to the class of substituted benzamides, it became possible to quantify extrastriatal dopamine receptors in living human brain. One of the most widely used radiotracers for the quantification of extrastriatal D_2/D_3 receptors is [$_{18}$F] fallypride ([18F]FP). It displays similarly very high affinities for D_2 and D_3 receptors and negligible affinity for any other abundant neuroreceptor. Although earlier PET studies with the moderate-affinity D_2/D_3 antagonist [$_{11}$C] raclopride ([$_{11}$C]RAC) demonstrated that the SGAs clozapine and quetiapine occupy striatal D_2/D_3 receptors to a significantly lesser extent than do other antipsychotics, it was later consistently shown in PET studies with high-affinity ligands that these 2 compounds nonetheless occupy a significantly higher proportion of temporolimbic than striatal D_2/D_3 receptors.

We have demonstrated that the clinical antipsychotic efficacy of clozapine is likely more related to its binding in temporal cortex than to its striatal binding. This Bpreferential[extrastriatal binding of SGAs, which was initially observed by Pilowsky et al, has since been shown for several other SGAs, at least to

a modest extent. The potential reasons for some controversial aspects of this phenomenon21 have been discussed previously.

To predict the appropriate clinical ziprasidone dose, receptor occupancy was initially characterized in [$_{11}$C] RACPET studies of normal volunteers. Because a single 60-mg dose of ziprasidone occupied 85% of striatal D_2/D_3 receptors, it was predicted that Ban effective antipsychotic dose will be between 20 and 40 mg.-$_7$Furthermore, a single low dose of ziprasidone evoked high occupancy (>70%) of cortical 5-HT_{2A} receptors. However, the antipsychotic dose in clinical studies was in fact 120 mg/d or more; doses of 40 mg/d or lower were not superior to placebo. It was subsequently determined that the D_2/D_3-receptor occupancy under steady state conditions in subchronically treated patients was lower than after acute administration. Thus, these results reveal an incongruity of the dopamine-receptor occupancy after single dose and steady-state treatment with ziprasidone. Apparently, single-dose PET experiments of ziprasidone D_2/D_3-receptor occupancies predicted much lower daily doses than were later found to be clinically effective.

To further characterize ziprasidone's extrastriatal binding and temporal changes in its binding in relation to its serum concentration, we performed PET studies with [$_{18}$F]FP in patients with schizophrenia at varying time points after the last drug administration. Furthermore, to investigate the basis of the discrepant effects of single versus multiple dosing, we used [$_{11}$C]RAC-PET to measure the occupancy of striatal dopamine D_2/D_3 receptors by acute ziprasidone or haloperidol in normal subjects.

Ziprasidone Occupancy After Single-Dose Treatment: The study was approved by the Joint Committee on Clinical Investigation and the Radiation Safety Committee. All participants gave written informed consent to be included. Administration of [$_{11}$C] RAC to the subjects was approved by the Food and Drug Administration.

Subjects: Four male healthy subjects (23–40 years; mean, 28 years) were included. All subjects underwent physical and mental-state examinations. No subjects with any mental and neurological disorder or relevant somatic diseases were included for participation in the single-dose study. Subjects had not recently taken medication with actions on the central nervous system. Each subject underwent 2 pairs of [$_{11}$C]RAC scans. A first baseline [$_{11}$C]RAC scan was followed by a second [$_{11}$C]RAC scan initiated 3 hours after administration of ziprasidone (40 mg, orally). At least 2 weeks later, the subjects underwent a second baseline scan followed by another [$_{11}$C]RAC scan 3 hours after haloperidol ingestion (7.5 mg, orally). The 3-hour interval was chosen because this duration approximates the t_{max} values of ziprasidone and haloperidol in young male subjects.

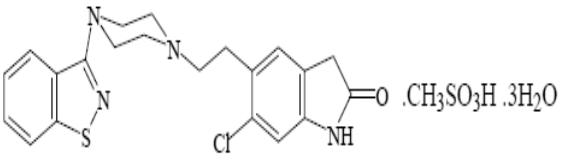
1.3 ZIPRASIDONE MESILATE

Ziprasidone hydrochloride is an antipsychotic agent for oral administration. It was first registered in October 2001. The current indications are (i) the treatment of schizophrenia, related psychoses, prevention of relapse and for maintenance of clinical improvement during continuation therapy; and (ii) as monotherapy for the short term treatment of acute manic or mixed episodes associated with bipolar I disorder.

Zeldox IM contains ziprasidone mesilate. A previous submission for registration of Zeldox IM was withdrawn by the sponsor after the ADEC recommended, and the Delegate proposed, rejection because efficacy in the proposed indication had not been satisfactorily established by an appropriately conducted placebo or active comparator-controlled study.

Other injectable antipsychotic agents with indications consistent with rapid control of agitation and disturbed behaviours in patients with psychoses include olanzapine, zuclopenthixol, droperidol, chlorpromazine and haloperidol.

The structure of ziprasidone mesilate trihydrate is shown below; it is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents.



ziprasidone mesylate trihydrate

The product is proposed to be supplied in a composite pack containing one vial of ziprasidone mesilate and an ampoule containing 1.2 mL of Water for Injection as diluent. The usual single dose is 20 mg, with a maximum daily dose of 40 mg. The drug substance and products are not the subjects of monographs in the BP, Ph Eur or USP. The drug substance is synthesised following a straightforward process from commercially available starting materials. The controls on starting materials, intermediates and reagents are satisfactory. Two polymorphs are known (A and B); the synthetic process has been shown to consistently produce Form A.

The specification was considered adequate to control the quality of the drug substance. In particular, limits for individual and total impurities were satisfactory.

Ziprasidone mesilate is very poorly soluble in water (~0.1%). For this reason, the product has been formulated with a substituted cyclodextrin excipient: sulfobutyl betadex sodium (SBECD). This excipient has a hydrophobic interior and a hydrophilic exterior and has the ability to form a noncovalent inclusion complex with ziprasidone. As the exterior of the substituted cyclodextrin is hydrophilic, this ziprasidone-cyclodextrin complex is much more water soluble than the drug alone. At the time of the original submission, SBECD was a new excipient for medicinal products in Australia.

SBECD is not a single compound but a defined reproducible mixture of β-cyclodextrins with varying degrees of substitution with sulfobutyl groups. Components with 2 to 10 sulfobutyl groups are present, with an average of 6.5 per cyclodextrin. The degree of substitution is adequately controlled in the excipient specification. SBECD is synthesised in one step from β-cyclodextrin and it is subject to comprehensive quality control testing. Limits for likely impurities.

are satisfactory. Formal stability trials have been carried out for SBECD and demonstrate that the excipient is highly stable.

Drug Product: Apart from nitrogen used as an inert headspace, the vial of drug contains no other excipients. The Water for Injection contained in the diluent ampoule meets compendial requirements and is satisfactory. The vial, closure and ampoule were evaluated by the Biocompatibility section of TGAL and were acceptable. The product is manufactured following a standard aseptic filtration procedure followed by lyophilisation. The diluent ampoules are aseptically filled and terminally sterilised following a standard procedure. No microbiological or endotoxin safety issues remain outstanding.

Although the stated dose per vial is 20 mg of ziprasidone, each vial contains the equivalent of 30 mg of drug (that is, a 50% overage). The company has argued that the overage is necessary as the high viscosity of the solution and the small vial size prevents the full volume being removed.

The company has provided satisfactory data to demonstrate the maximum volume that can be removed from the vial and the clinical evaluator has stated that there are no clinical concerns. There are therefore no objections to the inclusion of the overage. The specification is adequate to control the quality of the finished product. In particular, limits for degradation products were acceptable.

The stability data provided in the submission support the proposed shelf life for the composite pack of 24 months below 30°C. Satisfactory data have also been provided to demonstrate that the product is chemically stable when diluted as recommended in the Product Information. Bioavailability: A single bioavailability study was evaluated. This study was of randomised, open-label, single dose 3-way crossover design using 13 healthy male subjects, 12 of whom completed the 3 arms of the study.

The study compared the bioavailability of:

- An intramuscular injection of 5 mg ziprasidone.
- One capsule containing 20 mg ziprasidone taken immediately after a standard high-fat breakfast.
- An intravenous infusion of 5 mg ziprasidone over 60 minutes. The infusion was prepared by diluting the product to 0.083 mg/mL with sterile water.

The formulation of the IM injection and the 20 mg capsule were as proposed for registration (the capsule was the subject of a separate application) and there was a 7 day wash out period between each dose. Given the measured half-life of 3-4 hours, this was considered adequate.

Blood samples were taken before and regularly after each dose; the sampling times were considered adequate to describe the plasma concentration-time curve. Plasma samples were analysed using an acceptably validated HPLC method.

The data from this study show that the absolute bioavailability of a 5 mg intramuscular dose is approximately 100%, compared to about 60% for a 20 mg oral dose. Although Tmax was somewhat variable after IM injection (0.17-1.0 h), it generally occurred with 0.5 hours of dosing (8 out of 12 patients). Tmax following an intramuscular dose was about 7.5 hours earlier than after an oral dose.

The calculated half-life was somewhat longer after oral administration (3.8 h) than IM or IV (~3 h); this may reflect the long absorption time of an oral dose. It should be noted that this study investigated an IM dose of 5 mg, although the proposed dose by this route is 10-20 mg.

This original application was considered by the 79th (2001/4) meeting of the Pharmaceutical Subcommittee which raised no objections to registration provided all issues raised by TGA were satisfactorily resolved. The Subcommittee also requested that the company provide data on the maximum volume that can be removed from the vial and a number of amendments to the Product Information. The company has provided satisfactory data and has agreed to include the requested Product Information amendments.

Pharmacology : 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 α1-adrenergic receptors (Kis 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 norepinephrine. 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 in the acute control of the agitated psychotic patient is unknown. The mechanism of action of ziprasidone in schizophrenia, as with other drugs having efficacy in schizophrenia, is also unknown, however, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 ($5HT_2$) antagonism.

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 H1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of adrenergic α1 receptors may explain the orthostatic hypotension observed with this drug.

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A ($5HT_{2A}$) and dopamine type 2 (D_2) receptors. It is proposed that the antipsychotic activity is mediated, in part, through this combination of antagonist activities. Ziprasidone is also a potent antagonist at $5HT_{2C}$ and $5HT_{1D}$ receptors, a potent agonist at the $5HT_{1A}$ receptor and inhibits neuronal reuptake of norepinephrine and serotonin.

The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Ziprasidone is greater than 99% protein bound, binding primarily to albumin and α1-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 1.1L/kg when administered intravenously.

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 DRUG INTERACTIONS).

After ziprasidone is administered intramuscularly, approximately 20% of the dose is excreted in urine and approximately 66% is eliminated in faeces. Clinical Trails: Two pivotal, single-blinded, active comparator trials were conducted to compare the effects of ziprasidone IM to IM haloperidol in patients with acute exacerbation of schizophrenia or schizoaffective disorder. A multi-centre, parallel group study (1) compared ziprasidone IM (N=429) and IM haloperidol (N=138) administered for 1-3 days, followed by oral ziprasidone and haloperidol for another 6 weeks. The IM dosing was 10mg or 20mg ziprasidone or 2.5mg or 5mg haloperidol, administered at least twice. During the subsequent oral administration, the total daily ziprasidone dose was 80-160mg and the daily haloperidol dose was 5-20mg/day.

The other multi-centre, parallel group study (2) compared IM ziprasidone (N=130) and IM haloperidol (N=122) administered for 1-3 days, followed by oral ziprasidone and haloperidol for another 6 weeks. The IM and oral dosing regimens for ziprasidone and haloperidol are the same as the regimens in the other study.

In both studies, male and female subjects aged 18-70 years at the time of randomisation were eligible for inclusion in this study. Subjects had to meet Diagnostic and Statistical Manual (of Mental Disorders) (DSM)-IV criteria for schizophrenia or schizoaffective disorder. Subjects entering hospital (or in-patients transferring to a higher-dependency unit) within the previous seven days because of acute exacerbation of psychotic symptoms were included. Subjects had to have a minimum score of 40 on the

Brief Psychiatric Rating Scale (BPRS) scale (1-7) and agree to receive intramuscular medication for 1-3 days (at least two administrations).

Subjects were excluded if they were receiving concurrent treatment with antipsychotic agents at randomisation (within 12 hours prior to randomisation); for depot agents a period of two weeks or one cycle, whichever was the longer, had to occur between last administration and randomisation.

1.4 ROLE OF ZIPRASIDONE HYDROCLORIDE IN THE MANAGEMENT OF SCHIZOPHRENIA

Schizophrenia is a highly complex disorder characterized by positive symptoms (hallucinations, delusions, peech disturbance) and negative symptoms (social withdrawal, apathy, loss of emotional response) accompanied by marked impairments in social and cognitive function. The degree of suffering and disability is considerable with 80%–90% not working and in the 15–44 year old group, schizophrenia is considered one of the top ten causes of disease-related disability in the world.

The introduction of the atypical antipsychotics (also called second generation antipsychotics or SGAs) has changed the way we treat patients with schizophrenia. Despite a resurgence of interest in classical first generation antipsychotics due to their lower cost and comparable efficacy, atypical antipsychotics are now the preferred first-line treatments for schizophrenia by most clinicians, owing to their ability to manage effectively the positive and negative symptoms of schizophrenia with minimized EPS (extrapyramidal symptoms) and reduced risk of tardive dyskinesia.

However, even as use of second generation atypical agents increases, many psychiatrists still ponder the distinctions among the various atypical agents asking if these drugs are interchangeable and how differently they target the various symptoms associated with schizophrenia. In the absence of a critical mass of comparative data, the most relevant hypotheses for providing answers to these questions may be found through consideration of the psychopharmacologic binding properties as well as clinical trials results of individual atypical antipsychotic agents. Here we review these features of the atypical second generation antipsychotic ziprasidone.

Ziprasidone hydrochloride, a newer “atypical” or “second-generation” antipsychotic with many noteworthy receptor binding properties that contribute to its unique clinical profile, was approved by the US Food and Drug Administration (FDA) in 2001. It was first approved for the treatment of schizophrenia, and subsequently for acute mania or mixed states and then as adjunctive maintenance treatment of bipolar disorder when added to lithium or valproate-treated patients. Finally an intramuscular preparation was approved for acute agitation in schizophrenia as well.

Mechanism of Action: Ziprasidone is an atypical antipsychotic possessing a multireceptor-binding profile unique from that of any other antipsychotic agent in its class; the receptor-binding profile of ziprasidone may explain its performance in clinical studies and psychiatric practice. Ziprasidone, similar to most other SGAs, is a full antagonist of D2 dopamine receptors as well as 5HT2A (serotonin, 5HT, 5-hydroxytryptamine) receptors. All 5-HT2A/D2 antagonists share the same clinically ambitious goals: to quiet hyperactive dopamine neurons that mediate psychosis in the mesolimbic pathway, and to preserve physiologic function in dopamine neurons that regulate extrapyramidal movement and prolactin secretion respectively in the nigrostriatal and tuberoinfundibular pathway.

Ziprasidone has one of the highest 5-HT2A/D2 receptor affinity ratios and this has been correlated with a lower propensity for EPS and may also signify activity against the negative symptoms of schizophrenia and explain its proven antipsychotic effects and its possible antidepressant/anxiolytic effects. That said, SGAs are also a heterogeneous group of agents and beyond 5HT2A/D2 antagonism, ziprasidone acts at multiple serotonin receptors (not just 5-HT2A but also 5-HT1A partial agonism, 5-HT2C and 5-HT1D antagonism), has a unique blockade of monoamine transporters (5HT reuptake and NE reuptake) and lacks potent alpha1, muscarinic cholinergic M1 and histamine H1 antagonism. Potent 5HT1A partial agonist and 5HT2C antagonist actions may predict not only potential cognitive and affective actions of ziprasidone but also potential antidepressant and anxiolytic properties, due to the theoretical increases in dopamine and norepinephrine in prefrontal cortex. However, these properties have not been proven in controlled clinical trials. The 5HT2C antagonist actions of ziprasidone may also explain its activating actions when given in subtherapeutic doses. Ziprasidone’s affinity for the 5-HT2C receptor is 10 times more potent than its affinity for the D2 receptor.

Thus, low doses (eg, 40 mg/day) block 5-HT2C receptors but have little D2 receptor antagonism. On average, sufficient antagonism of D2 receptors for antipsychotic efficacy does not occur with ziprasidone until the dose reaches 120–160 mg/day. The differences in relative engagement of serotonin and dopamine receptors at different doses may explain why early “ activation” with ziprasidone is associated with lower doses (because blockade of 5-HT2C receptors can cause the release of dopamine in the brain) and then abates at higher doses (eg, 120 mg/day) when that effect is mitigated by D2 receptor antagonism. For this reason, ziprasidone’s activating actions may actually be diminished by increasing its dose, possibly due to recruiting substantial D2 antagonism.

Receptor type	Potential clinical implications of receptor activity
D2 antagonism	Positive symptom efficacy, EPS, endocrine effects
5-HT2A antagonism	Negative symptom efficacy, reduce EPS
5-HT2C antagonism	Sleep improvement, improved cognition, weight gain; activation, agitation
5-HT1A partial agonism	Short term: increased likelihood of agitation Long-term: antidepressant and anxiolytic activity
Alpha1-adrenergic antagonism	Postural hypotension
M1-muscarinic antagonism	Anticholinergic side effects (eg, cognitive impairment)
H1-histaminergic antagonism	Sedation, weight gain

Table: Receptors' Clinical Profile.

As far as adverse effects are concerned, the low H1 receptor antagonism of ziprasidone predicts generally low amounts of sedation; low affinity for alpha 1-adrenoreceptors suggests that ziprasidone is less likely to induce orthostatic hypotension and sedation; no significant affinity for muscarinic cholinergic receptors predicts a low propensity for anticholinergic side effects such as dry mouth, blurred vision, constipation, tachycardia and cognitive dysfunction.

The mechanism whereby some atypical antipsychotics mediate weight gain and dyslipidemia is unknown, but ziprasidone is among the agents (also including aripiprazole and lurasidone) least likely to have these side effects and has the reputation for being a more "metabolically friendly" drug.

Pharmacokinetic Profile, Metabolism and Dosing: Ziprasidone exhibits linear and predictable pharmacokinetics and has low potential for drug interactions; it is extensively metabolized after oral administration with only a small amount excreted unchanged in the urine (,1%) or feces (,4%), is highly protein bound (.99%) and its half life is about 6–7 hours reaching the steady-state plasma levels within 1–3 days. Age, gender, clinically significant cirrhosis (Child-Pugh A or B) and mild-to-moderate renal impairment have been shown to have no effects on the pharmacokinetic profile of ziprasidone.

Ziprasidone's oral bioavailability is 60% if taken without food: a meal equal to or greater than 500 kcal, irrespective of fat content, (eg, turkey sandwich and a piece of fruit) is required for optimal and reproducible bioavailability (100%) of the administered dose. The reason for this does not appear to be the fat content of the meal, but the bulk of the food, since keeping ziprasidone in the stomach for a longer period of time is what appears to be important as there is less absorption lower in the gastrointestinal tract.

This factor of requiring food for optimal absorption is a major issue in attaining a consistent clinical effect, since the amount of drug absorbed drops significantly if a patient stabilized on dosing with food then takes a dose without food.

Ziprasidone is metabolized by 2 major pathways: aldehyde oxidase and cytochrome P450 enzymes. About two thirds of ziprasidone metabolism is mediated by aldehyde oxidase, which has no known clinically relevant inhibitors or inducers. Approximately one third of ziprasidone's metabolism is mediated via CYP450-catalyzed oxidation through CYP3A4.

Neither CYP450 3A4 nor CYP450 2D6 inhibitors significantly affect ziprasidone plasma levels. Moreover, there is little potential to affect metabolism of drugs cleared by CYP450 enzymes. As ziprasidone, unlike clozapine and olanzapine, is not metabolized by CYP1A2, cigarette smoking (a CYP1A2 inducer) is unlikely to influence ziprasidone pharmacokinetics. According to the manufacturer (Pfizer) ziprasidone dosing in schizophrenia should be administered at initial oral dose of 20 mg twice a day; however, starting at 40 mg twice a day or 60 mg twice a day (this is considered the minimum effective dose) may be better tolerated in many patients, and then titrated to 80 mg twice a day in many patients. The best efficacy in schizophrenia and bipolar disorder is at doses .120 mg/day, but patients are often inadequately dosed in clinical practice.

Doses of 20–40 mg twice a day are not only too low for antipsychotic efficacy, but often activating and not well tolerated, perhaps due to potent 5HT2C antagonist properties. Paradoxically, such activation is often reduced by increasing the dose to 60–80 twice a day, perhaps due to increasing amounts of dopamine 2 receptor antagonism.

Even if some patients seem to respond better to doses .160 mg/day and up to 320 mg/day in two divided doses (ie, 80–160 mg twice a day) an increase to a dose greater than 80 mg twice daily is not generally recommended by the manufacturer as the safety of doses above 100 mg twice a daily have not been systematically evaluated in regulatory trials. Nevertheless, doses higher than 160 mg/day are often used in hospital settings and with severe patients but doses higher than 160 mg/day are considered off label as they are not approved doses by the FDA or other regulatory agencies. Rapid up-titration of ziprasidone to the optimal daily dose of 120–160 mg/day by day three of treatment is needed for optimum antipsychotic efficacy.

Some authors reported success with once daily ziprasidone usually at bedtime, but only when taking consistently with food and only in individuals taking doses, 160 mg/day.

For the intramuscular formulation (IM), recommended dose is 10–20 mg given as required; doses of 10 mg may be administered every 2 hours: doses of 20 mg may be administered every 4 hours; maximum daily dose is 40 mg intramuscularly; the intramuscular form should not be administered for more than 3 consecutive days. IM formulation can reduce agitation in 15 minutes. Ziprasidone intramuscular can be given short-term, both to initiate dosing with oral ziprasidone or another oral antipsychotic and to treat breakthrough agitation in patients maintained on oral antipsychotics.

1.5 ZIPRASIDONE NORDIC

Ziprasidone Nordic is presented in the form of capsules containing Ziprasidone hydrochloride which corresponds to 20 mg, 40 mg, 60 mg or 80 mg of the Ziprasidone. The excipients are lactose monohydrate, silica colloidal anhydrous and magnesium stearate. The capsule shell of the 20 mg, 40 mg and 80 mg capsules is consisted of titanium dioxide (E171), patent blue V (E131), black iron oxide (E172) and gelatine. The capsule shell of the 60 mg capsule is consisted of titanium dioxide (E171) and gelatine. The printing ink used for 20 mg, 60 mg and 80 mg capsules is consisted of shellac glaze, black iron oxide (E172) and propylene glycol whereas the component of printing ink used for 40 mg capsule are shellac glaze, propylene glycol, sodium hydroxide, povidone and titanium dioxide (E171). The capsules are packed in OPA/Alu/PVC/Alu blisters.

Ziprasidone hydrochloride is a creamy to slight pink crystalline powder which is practically insoluble in water. The structure of Ziprasidone hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

Ziprasidone Nordic capsules are formulated using excipients described in the current Ph Eur, except for some excipients in the ink compositions which are controlled according to the USP, NF, or relevant directives. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01). The ingredient magnesium stearate is of vegetable origin The product development has taken into consideration the physico-chemical characteristics of the active substance. The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with storage condition “Do not store above 30^0 C”.

Clinical Aspects: Absorption: Following oral administration of multiple doses of ziprasidone with food, peak serum concentrations typically occur 6 to 8 hours post-dose. The absolute bioavailability of a 20 mg dose is 60% in the fed state. Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food.

Elimination: The mean terminal half-life of ziprasidone after oral administration is 6.6 hours. Steady state is reached within 1-3 days. Approximately 20% of the dose is excreted in urine, and approximately 66% is eliminated in faeces. Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 20 to 80 mg.

To support the application, the applicant has submitted one bioequivalence study where Ziprasidone Nordic 20 mg hard capsule is compared to Zeldox 20 mg hard capsule under fed conditions. Biowaiver is requested for additional strengths, and the applicant was asked to justify the linearity of pharmacokinetics for the whole dose range 20-80 mg with literature references. Satisfactory response was given. The study was performed at Pharma Medica Research Inc. in Toronto, Canada, and GCP compliance for the clinical site has been confirmed. The study was a randomised, three-treatment, three-period, three-sequence single-dose crossover study conducted in 15 healthy volunteers comparing the reference product with two different batches of the test product. According to the applicant the data for one of the batches is to be considered as supportive information only. Bioequivalence was demonstrated for Cmax and AUC for both batches.

REFERENCES

- Delgado J N and Remers WA: Wilson and Griswold's Textbook of Organic Chemistry, Medicinal

and Pharmaceutical Chemistry. 1(P ed. Philadelphia; Lippincott Raven; 1992.

- Miller D: Remington- The Science and Practice of Pharmacy. 19" ed. Pennsylvania; MACK Publishing Company; 1995. p. 425. http; wikipe dia. org' wiki pipera zine.

- Alka Bali. Komal Sharma. Abhishek Bhalla. Simian Bala. Dinesh Reddy. Anant Singh Anil Kumar; European Journal of Medicinal Chemistry 2010; 45:2656-2662.

- Sushil Kumar. AK Wahi. Ranjit Singh: Tropical Journal of Medicinal Chemistry-2011:10(3):265-272.

- Mutlu Dilsiz Aytemir, Unsal Calis, Meral Ozalp: Synthesis and evaluation of anticonvulsant and antimicrobial activities of 3 -hydr oxy-6 -methyl-2 -substituted -4H-pyran -4-one derivatives. Arch Pharm Pharmaceutical Medicinal Chemistry 2004; 337:281-288.

- Mutlu Dilsiz Aytemir, Ebukekir Septioghi, Unsal Calis: Synthesis and anticomiilsant activity of new kojic acid derivatives. Arzneimittelforschung 2010; 60(l):22-29.

- Jacek Sapa. Barbara Filipek. Lesze K. Nowinski: Antiarrhythmic activities of 1 -[2 -hy droxy-3 -(4-phenyl-1 -pipera zinyl) propyl] -pyrr olidin-2 -one [MG- 1(RS)] and its enantiomers. Pharmacological Repoits 2011; 63:455-463.

- Ishwar J. Patil. Shailesh J. Parmar: Synthesis and studies of novel optically active Schiff s base derivatives and their antimicrobial activities. E. Joiunal of Chemistry 2010; 7(2):617-623.

- Agata Pietrzycka. Marek Stepniewski. Anna M Waszkielewicz and Hemyk Marona. Acta Poloriiae Pharmaceutica Drug Research 2006. 63(1): 19-24.

- A. Marzotto, D.A. Clemente, G. Valle, Acta Crystallogr. Sect. C 53 (1997) 1580.

- A. Marzotto, D.A. Clemente, G. Valle, Acta Crystallogr. Sect. C 54 (1998) 27.

- A. Ciccarese, D.A Clemente, F.P. Fanizzi, A. Marzotto, G. Valle, Inorg. Chim. Acta 275–276 (1998) 410.

- A. Ciccarese, D.A Clemente, F.P. Fanizzi, A. Marzotto, G. Valle, Inorg. Chim. Acta 275–276 (1998) 419.

- A. Ciccarese, D.A Clemente, F.P. Fanizzi, A. Marzotto, G. Valle, Acta Crystallogr. Sect. C 54 (1998) 1779.

- Newcomer, J. W., & Hennekens, C. H. (2007). Severe mental illness and risk of cardiovascular disease. Journal of the American Medical Association, 298,1794-1796.

- Saha, S., Chant, D., & McGrath, J. (2007). A Systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? Archives of General Psychiatry, 64(10), 1123-1131.

- Meyer, J. M., & Stahl, S. M. (2009). The metabolic syndrome and schizophrenia. Acta Psychiatrica Scandinavica, 119, 4-14.

- American Diabetes Association American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity. (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care, 27, 596-601.

- Hasnain, M., Vieweg, W. V. R., Fredrickson, S. K., Beatty- Brooks, M., Fernandez, A., & Pandurangi, A. K. (2009).

- Woodward, R.B.; Doering, W.E.; J. Am. Chem. Soc. 66, 1944, 849.

- Lewis, R.P.; Crit Care Med. 18, 1991, S5.

- Aggarwal, A.; Narcotic drugs 52, 1995.

- Brune, K.; Acute pain 1, 1997, 440.

- Foster, W.; Raoult, A.; JR Coll Gen Pract. 24, 1974, 889.

- Stern, A. M.; Markel, H.; Health affairs. 23, 2005, 611.

- Kostis, J. B.; New England Journal of Medicines. May. 2008, 431.

- Horacek, H.; Bubenikova, V.; Kopacek, M.; CNS Drugs 20, 2006, 389.

- Sneader, W.; Drug Discovery, 2005, 369.

- Craig, P. N.; Nodiff, E. A.; Lafferty, J. J.; Journal of Organic Chemistry, 22, 1957, 709.

- Bourquin, J. P.; Schwarb, G.; Gamboni, G.; Fischer, R.;Ruesch, L.; Guldimann, S.; Theus, V.;

Schenker, E.; Renz. J; Helvetica Chimica Acta, 41, 1958, 1072.

- Potoski, J.; Drug Discovery Today, 10, 2005, 115.
- Federsel, H. J.; Drug Discovery Today, 11, 2006, 966.
- Kumar, G.; Process Chemistry in the Pharmaceutical Industry, 1999.
- International conference on harmonization Q3A (R Guideline), Impurities in New Drug Substances, 7 February 2002.
- Wetzel, H.; Szegedi, A.; Hain, Ch.; Wiesner, J.; Schlegel, S.; Benkert, O.; Psychopharmacology, 119, 1995, 231.
- Green, B.; Curr. Med. Res. Opin, 15, 1999, 145.
- Edward, J. W.; Bernard, M. M.; Cyrus, J. O.; Ann L, L. N.; George, C. G; Frances, M. M.; Nelson, L. N; Karen, M. K.; J. Med. Chem., 44 (3), 2001, 372.
- Schmutz, J.; Kunzle, F.; Hunziker, F.; Bürki, A.; Helv. Chim. Acta., 48 (2), 1965, 336.
- Prakash Rao, S.H.; Senthil Kumar, S.P.: Journal of chemical sciences, 113 (3), 2001, 192.
- Grumann, A.; Huhta, S.; Rummakko, P.; PCT application, WO2005028457A1, 2005.
- Poornachander, T.; Srinivas Reddy, G.; Ramesh kumar, Anjaneyulu, Y.; Mukkanti, K.; Srinivasulu, B.; Satyanarayana, B.; Arkivoc, (Communicated).
- International conference on harmonization Q3A (R Guideline), Impurities in New Drug Substances, 2002.
- Chandra P.; Amin K.; Judith, G.; Keith, W.; Drug metabolism and disposition, 25, 1997, 863.
- Periyand, N.; Kilaru, S.; Thennati, R.; PCT application, WO 2003099198, 2003.
- Parthasaradhi, R. B.; Rathnakar, R. K.; Raji, R.R.; Muralidhara, R. D.; Srinivas, R., PCT application, WO 2006080025, 2006.
- Gurjar M. K.; Murugaiah, A. M. S.; Reddy, D.S.; Mukund, S.; Organic Process Research & Development, 7(3), 2003, 309-312.
- Poornachander, T.; Srinivas Reddy, G.; Ramesh kumar, Anjaneyulu, Y.; Mukkanti, K.; Srinivasulu, B.; Satyanarayana, B.; Organic chemistry-An Indian Journal, 6, 2010, 246.
- Venkatraman, S.; Rao, U.V.B.; Venkateshwarlu, M.; Vijayavardhan, C.; U.S. Patent Appl. 20060089502 A1, 2006.
- Prakash, C.; Kamel, A.; Anderson, W.; Howard, H.; Drug metabolism and disposition, 25(1), 1997, 206.
- Sharp, T.R.; Leeman, K.R.; Bryant, D.E.; Horan, G.J.; Tetrahedron Lett. 44, 2003, 1559.
- Singh, A.; Rao, B.M.; Deshpande, G. R.; Sangaraju, S.; Srinivasu, M.K.; Lalitha, D.M.; Satyanarayana, P.V.V.; Chandrasekhar, K.B.; Chromatographia, 2007, 191.
- Hach, C. C.; Banks, C. V.; Diehl, H.; Org. Synth., 1963, Coll. Vol. 4.
- Merck Index Drug No.785, Edition No. 14, 2006
- Oshiro, Y.T.; Sato, S.; Kurahashi, N.T.; European Patent. 0367141B1, 1996.
- Simpson, G. M.; Pi, E. H.; Sramek, J. J.; Drugs, 21, 1981, 138.
- Oshiro, Y.T.; Sato, S.; Kurahashi, N.T.; J. Med. Chem., 41, 1998, 658.
- Oshiro, Y.T.; Sato, S.; Kurahashi, N.T.; U.S. Patent 5006528, 1991.
- Ramakrishnan, A.; Subhash, V. D.; Dharmesh, G. P.; PCT Application WO 2007094009A1, 2007
- Briggs, J.R.; Whiteker, G.T.; Klosin, J.; PCT Application WO2005077884A2, 2005.
- Rajendiran, C.; Veera Reddy, A.; Subba Rao, A. V.; Jasti, V.; PCT Application, WO2004038220A1, 2004.
- Lansbury, P.T.; Mancuso, N.R.; Tetrahedron Letters, 29, 1965, 2445.
- Lee, B.S.; Lee, B.C.; Jun, J.G.; Chi, D.Y.; Heterocycles, 48(12), 1998, 2637.
- Lee, B.S.; Chi. D. Y.; Bull. Korean Chem. Soc., 19(12), 1998, 1373.
- Lee, B.S.; Chu, S.; Lee, I. Y.; Lee, B.; Bull. Korean Chem. Soc. 2000, 21(9), 860.

- Hino, K.; Nagai, Y.; Uno, H.; Chem. Pharm. Bull, 1988, 2386.
- Salama, P.; Jean-Francois, M.; Julie, L.; Yuan, W.; Wei, L.; US Patent application No. US20070032651A1, 2007.
- Poornachander, T.; Satyanarayana, B.; Ramesh Kumar, N.; Pratap Reddy, P.; Anjaneyulu, Y.; Synthetic Communications, 37, 2007, 4337. 83. Merck Index Drug No. 6822, 2006, 14th edition.
- Ichikawa, J.; Kuroki, T.; Kitchen, M. T.; Eur. J. Pharmacol, 287, 1995, 179.
- Chakrabarti, J. K.; Michael, H. T.; Edward, T. D.; EP patent No. 454436, 1991.
- David, O. C.; Fairhurst, J.; Bioorg. Med. Chem. Lett, 7 (1), 1997, 25-30.
- Majka, Z.; Tomasz, S.; Justyna, R.; Maciej, W.; PCT Application No. WO2004/000847 A1, 2004.
- Lenarsic, R.; Rok, Z.; Milena, B.; PCT Application No. WO2004/065390A1, 2004.
- Wang, Z.; PCT Application No. WO2004/094390 A1, 2004.
- Keltjens, R.; Antonius, P.T.H.; PCT Application No. WO2005/070939 A1, 2005.
- Jianguo, J.; Tao, L.; William, H. B.; Organic Lett, 5 (24), 2003, 4611.