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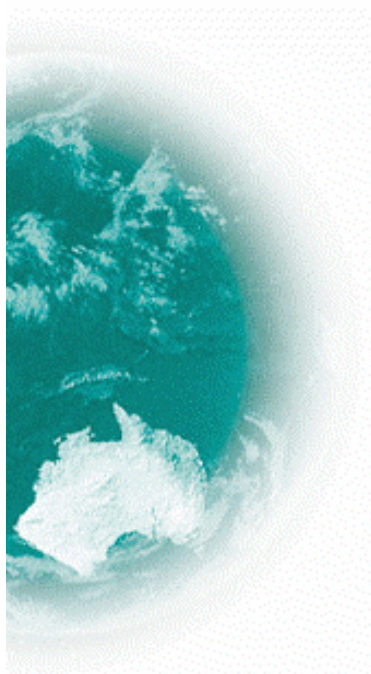
**Department of Health and Ageing
Therapeutic Goods Administration**

**Australian Public Assessment Report
for
Ziprasidone mesilate**

Proprietary Product Name: Zeldox IM

Submission No: PM-2008-1737-1

Sponsor: Pfizer Australia Pty Ltd



December 2009

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I. Introduction to Product Submission

Product Details

<i>Type of Submission</i>	New dosage form
<i>Decision:</i>	Approved
<i>Date of Decision</i>	28 October 2009
<i>Active ingredient(s):</i>	Ziprasidone (as the mesilate salt)
<i>Product Name(s):</i>	Zeldox IM
<i>Sponsor's Name and Address</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
<i>Dose form(s):</i>	Powder for injection
<i>Strength(s):</i>	20 mg
<i>Container(s):</i>	Vial of powder, plus ampoule of diluent
<i>Pack size(s):</i>	One vial and one ampoule per pack
<i>Therapeutic use:</i>	For acute treatment and short term management of agitation and disturbed behaviour in patients with schizophrenia and related psychoses when oral therapy is not appropriate
<i>Route(s) of administration:</i>	Intramuscular
<i>Dosage:</i>	10 mg every 2 hours or 20 mg every 4 hours, up to a maximum dose of 40 mg per day

Product Background

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 A previous submission for registration of Zeldox IM was withdrawn by the sponsor after the ADEC recommended, and the Delegate proposed, rejection because efficacy in the proposed indication had not been satisfactorily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.

Regulatory Status at the Time of Submission

This product is approved in the USA (2002), EU (2000) and NZ (2001). The application was withdrawn without prejudice by the sponsor in Canada (07 February 2007). In the EU, applications

made through a Mutual Recognition Procedure (2001-2002) were withdrawn by the sponsor in Belgium, France, Netherlands and the UK based on non-agreement; approval has not since been obtained.

Product Information

The approved product information current at the time this AusPAR was developed is contained at Attachment 1.

II. Quality Findings

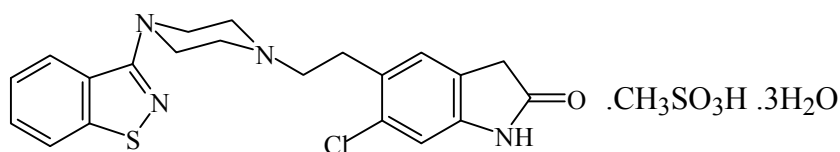
This application is a resubmission. The original application to register ziprasidone mesilate ("Zeldox IM") for injection was submitted on 31 October 2000. On 17 October 2001, following a negative ADEC recommendation, the sponsor withdrew the application.

Ziprasidone hydrochloride ("Zeldox") capsules 20, 40, 60 & 80 mg were subsequently registered.

Prior to consideration by ADEC, all chemistry and quality control issues relating to Zeldox IM had been satisfactorily resolved. None of the issues of concern to ADEC were related to the chemistry and quality control data.

Drug Substance (active ingredient)

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



ziprasidone mesilate 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 non-covalent 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 (including β -

cyclodextrin) 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 T_{max} 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). T_{max} 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.

Quality Summary and Conclusions

No significant changes have been made since the previous application to the drug substance or to the manufacture and specifications of the drug product.

The specification for the excipient, SBECD, has been amended: the limits for degree of substitution have been tightened for the genotoxic impurity, 1,4-butane sultone, has been tightened. The daily exposure to this substance at the maximum recommended dose of the drug product would be below the Threshold of Toxicological Concern, which is set at 1.5 µg in the CHMP *Guideline on the Limits of Genotoxic Impurities*.

SBECD also contains the impurity, 4-hydroxybutanesulfonic acid. The evaluator recognised the potential for this substance to cyclise to 1,4-butane sultone or to polymerise to other genotoxic mesilate esters during manufacture or storage of the finished product. Upon investigation, the sponsor found that the level of 1,4-butane sultone does indeed increase during storage of the product, although no evidence was found for the formation of dimers or oligomers of 4-hydroxybutanesulfonic acid. Based on the limited data available, the evaluator estimated that after storage for 3 years at 30°C (the originally proposed shelf life) the content of 1,4-butane sultone would correspond to 8.9 µg per 40 mg dose of ziprasidone. The Medicines Toxicology Evaluation Section estimated that an exposure of up to 12 µg per day would be acceptable given that Zeldox IM is not intended to be used for more than three consecutive days (see separate evaluation report). On this basis, the sponsor has been asked to apply an acceptable limit to 1,4-butane sultone. The sponsor considers that a limit five times this would be acceptable, but the company's arguments have been rejected by the Medicines Toxicology Evaluation Section. In view of the limited data currently available, the sponsor has agreed to a reduced shelf life of 2 years below 30°C.

Upon request, the sponsor also investigated the potential for formation of genotoxic mesilate esters (eg, methyl mesilate or isopropyl mesilate) from the mesilate part of the drug substance. The absence of these substances in the drug product was satisfactorily demonstrated.

There are no objections in respect of chemistry and quality control to registration of this product provided the sponsor agrees to apply an acceptable limit to 1,4-butane sultone. A shelf life of 2 years below 30°C is acceptable.

III. Non-Clinical Findings

Introduction

There were no nonclinical objections to the original registration submission for Zeldox IM, which was withdrawn by the sponsor following a negative ADEC recommendation based primarily on clinical deficiencies (efficacy, pharmacokinetics and renal safety). However, issues were raised by the nonclinical evaluator may have contributed to the negative ADEC recommendation:

- The nonclinical safety of the excipient SBECD, with particular reference to nephrotoxicity at levels close to the proposed clinical dose.
- Comparative toxicity of the mesilate and hydrochloride salts.

The current submission comprised a summary of additional nonclinical studies with SBECD which further characterise the toxicity of this excipient. Studies in support of the mesilate salt included 2

repeat dose studies which had been submitted previously and a comprehensive set of reproductive and developmental toxicity studies. All submitted studies were GLP-compliant. Additional data relevant to the current application are the toxicological profiles of ziprasidone hydrochloride and SBECD in previous submissions.

Pharmacology

Ziprasidone is a dopamine and serotonin receptor antagonist. As discussed in the previous application for Zeldox IM, no nonclinical studies have been performed comparing the pharmacological activity of the hydrochloride and mesilate salts of ziprasidone and the efficacy of the mesilate salt has not been tested in a validated animal model of agitated psychotic behaviour (the proposed indication). Thus, evidence of the pharmacodynamic efficacy of ziprasidone mesilate for the proposed indication needs to rely on clinical data. SBECD has been included in the IM formulation to enhance the solubility of ziprasidone mesilate in this formulation.

Pharmacokinetics

As noted in the previous submission, a comparison of the metabolic profiles following IM and PO administration of the different ziprasidone salts has not been determined in any animal species. However, as the bioavailability following IM administration of ziprasidone mesilate at least in dogs is essentially complete, no additional metabolites would be expected by the administration route compared with the oral route.

Toxicology

Ziprasidone

The toxicity of ziprasidone mesilate/SBECD following IM administration was examined in two repeat dose studies in rats and dogs with treatment duration of 28 days, submitted and evaluated previously. Based on the previous evaluator's recommendation with the acknowledgement that systemic ziprasidone exposure at the maximal recommended daily IM dose of the mesilate salt is about half that at the maximal recommended PO dose of the hydrochloride, there was no evidence of a change in the safety profile of ziprasidone with the new formulation.

SBECD

Nonclinical studies of SBECD suggested potential renal toxicity of this excipient, with exposures at the threshold and NOEL doses close to the estimated clinical exposure at the maximal recommended human dose. All of the effects were reversible except epithelial vacuolation of urinary bladder, with exposure ratios of 16 in rats and 4-8 in dogs for the lowest tested doses inducing non-reversible changes.

Additional nonclinical study reports of SBECD submitted with the current application conveyed consistent findings to those reported previously: renal tubular vacuolation, vacuolation of transitional epithelium of the renal pelvis and urinary bladder, with associated urinalysis and serum chemistry indicators of renal toxicity in mice (1200 mg/kg/day SC), rats (≥ 600 mg/kg/day IV) and monkeys (≥ 5600 mg/kg/day IV). Vacuolation of hepatocytes, foamy macrophages in various organs (lungs, lymph nodes, testes, spleen), and inflammation and infection at the injection site were also observed in mice (1200 mg/kg/day SC), rats (≥ 600 mg/kg/day IV) and monkeys (≥ 900 mg/kg/day IV, 120 mg/kg/day SC). There were no additional findings in the newly submitted studies that altered the toxicological profile of SBECD. The studies evaluated for the original application indicated that the NOEL for renal toxicity was 80 mg/kg/day for rats with an estimated exposure similar to that anticipated clinically from the maximum recommended dose of Zeldox IM and the NOEL for other toxicities was approximately 6 times the anticipated clinical exposure. The mechanism of nephrotoxicity of SBECD appeared to be consistent with the class of cyclodextrins and occurred as a result of accumulation and crystal formation in the renal proximal tubular epithelial cells and subsequent lysosomal activity.

Based on the short duration of administration (≤ 3 days), the level of SBECD in Zeldox IM compared with approved SBECD-containing formulations (including a product with a similar indication), and the additional nonclinical information provided by the sponsor, there are no objections to the proposed SBECD dose. However, the effect of SBECD in patients with renal impairment needs to be addressed by clinical data.

Genotoxicity and carcinogenicity

Ziprasidone hydrochloride was non-genotoxic but induced pituitary adenomas and mammary adenocarcinomas in female mice as a result of pharmacological action. Due to species differences in the role of prolactin this is not considered clinically relevant. SBECD was non-genotoxic although it does contain the genotoxic impurity 1,4-butane sultone. Genotoxicity and threshold levels are discussed below (see impurities). No carcinogenicity studies with ziprasidone mesilate/SBECD or SBECD alone have been submitted.

Reproductive toxicity

No reproductive and developmental toxicity studies of ziprasidone mesilate formulated with SBECD were submitted with the previous application. Ziprasidone crosses the placenta and both ziprasidone and SBECD affect embryofetal and/or postnatal development. As the presence of SBECD could alter the tissue distribution pattern of ziprasidone, and as the 2 compounds could also have synergistic adverse effects, additional reproductive toxicity studies with ziprasidone mesilate + SBECD were conducted. All studies included control groups receiving sterile water and SBECD; no significant differences were reported between the two control groups.

In a fertility study, female rats treated IM with ziprasidone mesilate/SBECD showed disruption to oestrous cycling, consistent with previous findings with oral ziprasidone hydrochloride. A No Adverse Effect Level (NOAEL) was therefore not established, but the NOAEL for female fertility/early embryonic development was 20 mg/kg/day IM (estimated AUC_{0-24h} 11 $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} = 6$). With ziprasidone hydrochloride PO previously (SN 99-2149-1), female rat fertility was impaired at 160 mg/kg/day (8x MRHD, mg/m^2), with a NOEL of 40 mg/kg/day. The prolongation of oestrous cycling from ziprasidone is likely to be a pharmacological effect as serotonin and dopamine antagonists have been shown to block ovulation and disrupt oestrous cycling in rodents (Hoekstra *et al.*, 1984; Dominguez *et al.*, 1987). The clinical significance of this is unclear due to species differences in the role of prolactin. However, it is clear from the data presented that there was no difference in the effects on female fertility between the two formulations of ziprasidone. Fertility in male rats was not affected following ziprasidone mesilate/SBECD up to 20 mg/kg/day IM (estimated AUC_{0-24h} 11 $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} = 6$), as also reported previously following ziprasidone hydrochloride 160 mg/kg/day PO.

There was no evidence of teratogenicity in rats following IM administration of ziprasidone mesilate/SBECD up to 40 mg/kg/day (AUC_{0-24h} 19 $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} = 11$). Reduced fetal weights attributed to maternotoxicity were observed from dams treated with ≥ 10 mg/kg/day IM ($AUC_{0-24h} = 4.8$ $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} = 3$), with the NOEL at 2 mg/kg/day ($AUC_{0-24h} = 1.4$ $\mu\text{g}\cdot\text{h}/\text{mL}$, ER_{AUC} approximately 1). A similar profile was reported for oral ziprasidone hydrochloride in pregnant rats, with the only adverse effects attributable to maternotoxicity.

Renal and cardiovascular teratogenic effects have been observed in rabbits treated with ≥ 30 mg/kg/day PO ziprasidone hydrochloride ($3\times$ MRHD, mg/m^2), with a NOEL of 10 mg/kg/day PO (SN 99-2149-1). These effects were not observed in the new studies with ziprasidone mesilate/SBECD up to 10 mg/kg/day IM ($AUC_{0-7h} = 5$ $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} = 3$), although an increase in the developmental variation “*vertebral arches fused to pelvis*” was noted in fetuses from rabbits treated with ≥ 5 mg/kg/day IM ($AUC_{0-7h} = 3$ $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} = 2$); the NOEL was 1 mg/kg/day IM ($AUC_{0-7h} = 0.5$ $\mu\text{g}\cdot\text{h}/\text{mL}$, $ER_{AUC} < 1$). As with the renal and cardiovascular effects following PO dosing, there was no indication that this was related to maternal toxicity. Toxicokinetic data with PO ziprasidone in rabbits were not reported in the earlier study and therefore a comparison of

exposures obtained from PO and IM treatments in pregnant rabbits cannot be performed, although the ERs for developmental effects based on AUC and mg/m² MRHD are not dissimilar and are close to the clinical exposure/dose.

In pre/postnatal studies in rats, findings observed with ziprasidone mesilate/SBECD IM were consistent with those reported previously with ziprasidone hydrochloride PO, with increased stillbirths, reduced postnatal survival, reduced birth weights which were sustained into adulthood and increased motor activity in F₁ offspring. The NOAELs for F₁ offspring were 5 mg/kg/day PO (< MRHD, mg/m²) and 2 mg/kg/day IM (AUC_{0-24h} = 1.2 µg.h/mL, ER_{AUC} = 0.7), and the effects are likely to be related to maternal toxicity and subsequent neglect.

Studies conducted with SBECD alone were evaluated in the previous submission including a fertility/reproductive performance study in rats (up to 1500 mg/kg/day IV), embryofetal development studies in rats (up to 3000 mg/kg/day IV) and rabbits (up to 1500 mg/kg/day IV), and a pre/postnatal study in rats (up to 3000 mg/kg/day IV)¹. The only treatment-related effects on reproductive parameters were found in the pre/postnatal study, where increased stillbirths and reduced viability and pre-weaning body weights in F₁ pups (at 3000 mg/kg) were attributed to maternal toxicity. A NOAEL of 600 mg/kg/day IV was obtained. Assuming identical pharmacokinetics between IV and IM administered SBECD, this dose is 20 fold higher than SBECD in the ziprasidone mesilate/SBECD IM NOAEL dose, indicating that the adverse F₁ effects from ziprasidone mesilate/SBECD are attributable to the active rather than the excipient. Based on similar toxicities observed at similar exposures (see above), there appears to be no additional concerns for F₁ offspring with the ziprasidone mesilate/SBECD formulation compared with the registered capsule formulation. Even so, the NOAEL exposures are close to the clinical exposure, reinforcing the recommendation that ziprasidone as either the oral or IM formulation should not be used in pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

Local tolerance

Whilst there was some evidence of skin sensitisation in guinea pigs with SBECD, there was no evidence of hypersensitivity reactions in repeat dose toxicity studies either alone (IV) or with ziprasidone mesilate. Therefore, while the potential for allergic reactions from IM administration of SBECD-containing formulations was noted in the previous evaluation report, there are no further supporting indicators.

The local tolerance of IM injections of ziprasidone mesilate with SBECD were examined in the previous application. The combined formulation caused myofibre necrosis and inflammation at the injection site of rabbits, observed at doses marginally higher than the clinical IM dose of 20 mg ziprasidone (+ 294 mg SBECD) with some evidence of repair by 7 days. The previous evaluator suggested that, "*clinically it might be wise for any subsequent injections to be given in different IM sites*". Data submitted with the current application do not alter this recommendation.

Impurities

A discussion of the impurities of ziprasidone and their qualification is contained in previous nonclinical evaluation reports. The excipient SBECD contains residual levels of the impurity 1,4-butane sultone, a known alkylating mutagenic agent with evidence for carcinogenicity in rodents (Kohlpoth *et al.*, 1999; Druckrey *et al.*, 1970; Osterman-Golkar and Wachtmeister, 1976). No carcinogenicity studies with SBECD (containing 1,4-butane sultone) were performed and the longest repeat dose toxicity studies performed with SBECD were 6 months in mice and rats and 1 year in monkeys. Though there were no tumours reported in these studies, there is insufficient

¹ Evidence of SBECD toxicity was seen in treated animals (renal tubular vacuolation, foamy macrophages, kidney discolouration).

information provided to determine the carcinogenic potential of the proposed limit for 1,4-butane sultone.

The sponsor states that they have made efforts to reduce the level of 1,4-butane sultone. Assuming a MRHD of Zeldox IM, consisting of 588 mg/day SBECD, a maximum daily dose of approximately 0.6 µg 1,4-butane sultone would be expected. According to Guideline CPMP/SWP/5199/02², this is below the Threshold of Toxicological Concern (that is, 1.5 µg/day). A review of appropriate literature suggests the proposed level of 0.6 µg/day is appropriate. However, the quality evaluator noted the potential of an additional impurity, 4-hydroxybutane sulfonic acid, to undergo internal esterification to give 1,4-butane sultone, thereby exceeding an acceptable limit during storage. Based on data from aged batches and extrapolating for 3 year storage, the exposure to 1,4-butane sultone could be considerably greater.

According to EMEA/CHMP/SWP/431994/2007³, for durations of exposure that are in excess of 1 day but no longer than 1 month, an acceptable daily intake of genotoxic impurities would be 60 µg/day (or 39.6 µg/m²/day on a body surface area basis using a mg/kg to mg/m² conversion factor of 33 for a 50 kg individual). Given that the NOEL for tumours after IV administration of 1,4-butane sultone was 25.7 mg/m²/day to rats, 650-fold higher than the proposed limit of 60 µg/day, there is a case for considering that this limit of 60 µg/day may be appropriate. However, long-term SC or PO dosing of rats with similar doses of 1,4-butane sultone was found to be carcinogenic (no NOEL established), including tumours at the administration site. Unfortunately, carcinogenicity studies following IM administration have not been performed. In view of the data limitations, an estimate of acceptable exposure to 1,4-butane sultone can be made by extrapolating from the no-significant-risk-level (NSRL) of 0.3 µg/day proposed for 1,3-propane sultone, adjusted for the known differences in mutagenicity between the two compounds. Thus, a similar frequency of mutants in reverse mutation assays was reported for a 1,4-butane sultone concentration 41x that of 1,3-propane sultone. As an added conservative measure, this limit is also contingent upon the limited (3 days maximum) duration of exposure.

Non-Clinical Summary and Conclusions

With the exception of the excipient SBECD, there were no additional toxicological concerns with the proposed new dosage form, salt and administration route (20 mg/mL powder for injection; mesilate salt; IM) of ziprasidone compared with the registered oral ziprasidone hydrochloride product (Zeldox capsules), based on repeat dose and reproductive studies.

SBECD has shown renal toxicity in repeat dose nonclinical studies at exposures about twice the clinical exposure at the MRHD. SBECD also contains an impurity 1,4-butane sultone, a mutagen and rodent carcinogen. SBECD is currently contained in 2 registered products at equal or much higher daily doses.

Findings in specific local tolerance studies suggested that, clinically, multiple injections (if required) should be given at different sites.

There are no nonclinical objections to the proposed registration of Zeldox IM for short-term (≤ 3 days) use.

² CPMP/SWP/5199/02 – Guideline on the limits of genotoxic impurities.

³ EMEA/CHMP/SWP/431994/2007 – Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities.

IV. Clinical Findings

Introduction

The contents of the original submission were as follows:

Single Dose Kinetics Ziprasidone after I.M. Injection:

- Study 128-033: randomised, placebo controlled study in healthy volunteers,
- Study 128-038 randomised, single-blind, placebo controlled study in healthy volunteers.

Tolerability, Kinetics of I.M. Ziprasidone after Multiple Doses:

- Study 128-046 3-day randomised, single-blind, placebo controlled study in DSM-III-R schizophrenia, schizoaffective or schizotypal personality disorder.

Comparing Efficacy, Safety two doses I.M. Ziprasidone in Psychosis:

- Study 128-125 multi centre, double-blind randomised, parallel group study in DSM-IV psychotic disorder; 24 hour study in agitation,
- Study 128-126 multi centre, double-blind, randomised, parallel group study in DSM-IV psychosis with agitation; 24h treatment period.

Assessing Safety, Tolerability of I.M. ziprasidone in Non-Organic Psychosis:

- Study 128-306 open label, parallel group study in acute psychosis; 3 days I.M. followed by 4 days p.o.; randomised 2:1 to ziprasidone: haloperidol.

Assessing Safety, Tolerability of Ziprasidone in Psychosis:

- Study 128 - 120 open label study in DSM-III-R schizophrenia (acute episode); 3 days of I.M. ziprasidone followed by 2 days p.o.
- Study 128 - 121 open label, parallel group study in DSM-III-R psychosis; 3 days IM followed by 4 days p.o.; randomised 2:1 to ziprasidone:haloperidol.

The current submission included:

- Study ZIP-NY-97-001: A multi-centre, parallel group comparison of efficacy and safety in acutely agitated patients with schizophrenia or schizoaffective disorder between IM ziprasidone (10 mg or 20 mg N = 429) and IM haloperidol (2.5 mg or 5 mg N = 138) administered for 1-3 days, followed by oral ziprasidone and haloperidol for a total treatment duration of 6 weeks.
- Study A1281050: A multi-centre, parallel group comparison of efficacy and safety in acute exacerbation of schizophrenia and schizoaffective disorder between ziprasidone IM (10 mg or 20 mg N = 130) and IM haloperidol (2.5 mg or 5 mg N = 122) administered for 1-3 days, followed by oral ziprasidone and haloperidol for a total treatment duration of 6 weeks.
- Study A1281063: A randomized, single-blind, 2-treatment study in schizophrenic patients of the pharmacokinetics and QTc effects of ziprasidone IM (first 20mg, then 30 mg) and haloperidol IM (first 5, then 7.5 mg).
- A population pharmacokinetic (PK) analysis of data from 4 Phase 1 ziprasidone IM studies (128-033, -037, -038 and 046) and 5 Phase 3 IM studies (128-120, -121, -125, -126 and -306) to evaluate the PKs and the effects of covariates such as age, renal dysfunction and hepatic dysfunction. A review of this analysis, but not the full report, was with the original submission.

Pharmacokinetics

The Delegate's pre-ADEC overview for the original submission contained the following concerns:

1. There are no data on C_{max} values after repeated IM administration. The PK repeat dose study failed to define the C_{max} values due to limited sampling. This data is important given the known effect on QT_c prolongation of ziprasidone.
2. There were no data on the metabolism of ziprasidone when given IM. The data from the oral ziprasidone application indicate that ziprasidone is extensively hepatically metabolised in humans. Consequently, after IM administration a greater fraction of unchanged ziprasidone will enter the systemic circulation than after PO administration.
3. There were no PK data on interactions between ziprasidone and other drugs.
4. In particular there were no PK data on patients stabilised on oral ziprasidone who were treated with IM ziprasidone subsequent to becoming agitated.
5. There were no PK data on the effect of ziprasidone IM in patients with hepatic or renal impairment or in patients aged > 65 years or in children or on sex differences. There were only 5 females included in the PK studies with ziprasidone mesilate IM.

Oral bioavailability may be as low as 30%, bioavailability of 100% is claimed for the IM preparation.

Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide (M10) and S-methyl-dihydroziprasidone (M9).

Study A1281063

There was one additional PK study submitted - Study A1281063 - a randomized, single-blind, 2-treatment PK & PD study in schizophrenic patients with haloperidol as active comparator. After being tapered to the lowest possible dose of their current antipsychotic over approximately 7 days, then following a 4-day washout of existing antipsychotics subjects received either ziprasidone - 20 mg IM then an additional 30 mg IM four hours later [M/F: 25/6 - completed: 25, mean age 43.0years (range 25-59y)] or haloperidol - 7.5 mg IM then an additional 10 mg IM four hours later [M/F: 21/6 - completed: 24, mean age 43.6years (range 21-72)]. This study is summarised in Table 1.

Table 1. Pharmacodynamic study: A1281063

Design; Study population; PD methods	Subjects; Treatment; Dose, Duration	PD Results	Safety
Phase 1 Multicentre, Single blind, parallel group, multiple dose study to characterize the PKs and QTc effects of IM ziprasidone or IM haloperidol in subjects with schizophrenia or schizoaffective disorder	<p>After being tapered to the lowest possible dose of their current antipsychotic over approximately 7 days, then following a 4-day washout of existing antipsychotics subjects received either</p> <p>Ziprasidone - 20 mg IM then an additional 30 mg IM four hours later.</p> <p>Randomized: 31 Treated: 31 Completed: 25</p> <p>M/F: 25/6 Mean Age 43.0years (range 25-59y)</p> <p>or</p> <p>Haloperidol - 7.5 mg IM then an additional 10 mg IM four hours later.</p> <p>Randomized: 27 Treated: 27 Completed: 24</p> <p>M/F: 21/6 Mean Age 43.6years (range 21-72)</p>	<p>Both treatment groups demonstrated comparable mean increases in QT_c after both the first and second injections. No subject in either treatment group had a QT_c interval ≥ 480 msec. 1 patient after the second ZIP injection had a QT_c ≥ 450msec</p> <p>After the first injection 12/25 ZIP & 13/24 HAL had a Δ QT_c ≥ 30msec.</p> <p>After the second injection 18/25 ZIP & 14/24 HAL had a Δ QT_c ≥ 30msec., with 1 Zip patient with a Δ QT_c ≥ 60msec.</p>	<p>3 discontinued due to AEs (2 ZIP extrapyramidal syndrome; hypotension and dizziness; 1 HAL extrapyramidal syndrome).</p> <p>1 SAE was post-therapy (HAL: depression, increased, severe psychosis).</p> <p>1 HAL patient had severe extrapyramidal syndrome;</p> <p>Other AEs were mild or moderate.</p>

In the newly submitted study (063) T_{max} was 1.2h after the first injection and 1.1h after the second. The mean in previously assessed studies (033 & 038) in healthy volunteers was 0.7h.

Study 063 also measured plasma concentrations of S-methyl-dihydroziprasidone (M9), and ziprasidone sulphoxide (M10). T_{max} for these metabolites after the first injection was 2.9h (M9) and 2.11h (M10) with C_{max} increasing 2-3 fold after the second injection (M9 4.17 rose to 12.9ng/mL; M10 10.8 rose to 21.6ng/mL).

In study 063 T_{1/2} for ziprasidone mesilate was 5.0h range 3.3-9.1h (from the previous evaluation in volunteers T_{1/2} was 2-6h in study 033 and 1.76 – 3.52h in study 046 and was independent of the dose administered).

Apparent plasma clearance was calculated in the previous evaluation to be 18.9-24L/h and independent of dose.

The previous evaluator stated that the mean terminal half life on day 3 appeared to be longer than on day 1 (7-13h vs. 3-5h). This was attributed to the longer plasma sampling schedule on day 3 compared to day 1.

The results from study 063 were used to calculate PK parameters.

Pharmacokinetics at Steady State

Multiple dose kinetics

Previously, based on an underestimated AUC in patients, the accumulation ratio Day 1 to 3 was < 1.

In study 063 C_{max} after the first injection was 182ng/mL (range 87-300ng/mL), C_{trough} was 64.2ng/mL at 4h after the initial injection, with after the second injection. C_{max} 319ng/mL (range 134-637ng/mL). The increased C_{max} after the second injection was 1.8 times the first C_{max} .

24h ziprasidone concentrations were mean 7.1ng/mL (range 2-13ng/mL), i.e. at the earliest recommended time of subsequent injection (4h) some accumulation does occur but this would appear to be unlikely to be a problem over the maximum 3 day regimen proposed.

Both metabolites M9 and M10 are of concern in that like ziprasidone, they are expected to prolong QT_c . M10 has a similar $T_{1/2}$ to ziprasidone, but M9 with a $T_{1/2}$ of 20.1 h would be expected to accumulate more. After an initial concentration of 4.17ng/mL, the concentration at 24h is above 0.8ng/mL. However, given the usual extensive first pass metabolism with oral therapy (up to 70% fasted), it is assumed that patients on oral ziprasidone would have experienced greater exposure, so this accumulation over 3 days is unlikely to be a problem.

The previous Delegate commented on the lack of data on C_{max} values after repeated IM administration. Study 063 added information on repeated dosage over 24h, and given the proposed PI Dosage of up to 3 days use at 40mg/day, extrapolation of results to maximum recommended duration would appear reasonable. The bioavailability of the drug was shown to be approximately 100% in study 128-037.

Pharmacokinetics in Special Populations

Renal impairment, Hepatic impairment and the elderly

While not in the population PK report, the Clinical Overview points out that renal and hepatic impaired patients were excluded and elderly patients were not well represented in the studies used for the population PK report.

The submission included a population pharmacokinetics report using subjects combined from previous studies. 483 subjects – 436 were patients, M/F 401/82, mean age 38.0 ± 12.6 years (range 18 – 76y), mean weight $82.0\text{kg} \pm 16.4$ (range 40.8 - 154.2kg). Ziprasidone concentration data were analysed using an extended least squares algorithm which used mixed effects models to describe PK observations by modelling both fixed effects such as dose, time, PK parameters such as clearance, volume of distribution, absorption coefficient, and absorption lag times, as well as parameters that measure the influence of covariates such as age and body weight, and two types of random effects: 1) the inter-individual variability (h) in model parameters across the population sampled and 2) the residual intra-subject variability due to random fluctuations on an individual's parameter values and measurement errors such as inaccuracies in recording time of dosing or sample collection, assay errors, and model specification error.

The base PK model identified was comprised of 2 compartments with combined zero and first order absorption terms. With this model, no systematic deviations were observed over the range of ziprasidone exposures.

This model indicated that apparent systemic clearance (CL/F) was linearly related to body surface area and volume of distribution of the central compartment (V_c/F) was linearly related to subject weight. Clearance is independent of dose. This is consistent with ziprasidone being eliminated primarily by hepatic metabolism and its volume of distribution is a function of the size of the individual. Individual clearance estimates generated with this model were independent of dose with median values ranging from 23.9 to 25.9 L/hr over the dose range.

Addition of gender to this model with respect to CL/F produced a change in the objective function indicating significance, however, the range of its standard error confidence interval was sufficiently close to including zero to warrant exclusion of this covariate variable. Gender was not related to V_c/F .

Age, race, gender, and benzodiazepine use, as well as creatinine clearance, serum creatinine, total protein, serum albumin and direct bilirubin values did not significantly correlate with ziprasidone PK parameters. No correlation was observed between baseline values of aspartate aminotransferase and alanine aminotransferase and ziprasidone PK parameters, (in the restricted population studied).

Summary

This submission has addressed the lack of data on C_{max} values after repeated IM administration (study 063 used 20 + 30 mg in 24h), as well as the lack of data on the metabolism of ziprasidone when given IM.

It is now possible to estimate that accumulation with a maximum of 40 mg per day over 3 days is unlikely to be a problem. In the short term (that is 2 x 4 hourly injections), however there is some accumulation with C_{max} almost doubling (1.8 x). The lack of first pass metabolism but otherwise similarity to the oral form can be seen. The population PK study is not overly helpful in relation to patients with hepatic or renal disease.

The lack of PK data on patients stabilised on oral ziprasidone who were treated with IM ziprasidone subsequent to becoming agitated was not addressed.

Drug Interactions

There were no new data. The sponsors had submitted in the earlier application in reply to a question on drug interactions that because of the lack of a first pass effect interactions through effects on CYP3A4 would be expected to be less.

Pharmacodynamics

Pharmacodynamic Effects

QT Prolongation

In **Study 054** oral ziprasidone 160 mg/day (top clinical dose) prolonged QT_c by 15.9 msec and in the presence of a metabolic inhibitor ketoconazole (with a 39% higher serum ziprasidone concentration), QT_c was prolonged by 16.6 msec.

In **other studies**, prior to study 063, some QT_c prolongation was noted in both IM ziprasidone and in the active comparator groups.

Mean QT_c change for all IM ziprasidone doses ≥ 5 mg was 0.1 msec vs. a mean change of 0.6msec for IM haloperidol. There were no QT_c values > 500 msec with IM ziprasidone. QT_c values ≥ 450 msec were infrequent (1.1% with ziprasidone, 1.3% with haloperidol).

Study 063 In previous ziprasidone studies, one QT and RR interval pair per subject was measured for the baseline QT correction factor. Study 063 collected 27 baseline QT and RR interval pairs per subject over 24 hours prior to dosing. Analysis showed high intra-subject variability in slopes for estimating the baseline QT correction factor due to the narrow range of RR intervals in each subject and/or, potentially, to changes in vagal tone that might take place during the course of a day.

While standard correction for heart rate was applied to get QT_c values, the change in QT_c from baseline was further corrected. This was done by using as baseline comparator the QT_c measurement obtained at the same time in the previous (baseline) 24h that the result observation was taken (described as time-corrected). All results in the report were so corrected (i.e. for rate and effect of time of day) except for the reports of actual QT_c by category which related to one patient. (No subject in either treatment group had a QT_c interval ≥ 480 msec. 1 patient after the second ziprasidone injection had a $QT_c \geq 450$ msec).

Both treatment groups demonstrated comparable mean increases in QT_c at their respective C_{max} values after both the first and second injections. At ziprasidone C_{max} for each individual (time-corrected), changes in QT_c were 4.6 msec and 12.8 msec. For haloperidol at C_{max}, changes in QT_c were 6.0 msec and 14.7 msec.

Maximum (time-corrected) mean changes from baseline in QT_c were for ziprasidone at 2h 10.9 ± 13.4, at 4.5h 16.7 ± 17.2 and at 5.75h 17.1 ± 16.8.

Maximum (time-corrected) mean changes from baseline in QT_c were for haloperidol at 1.5h 14.1 ± 14.3, 2h 14.9 ± 15.9, 4.75h 17.8 ± 16.9 and at 6h 17.2 ± 14.3.

After the first injection 12/25 ziprasidone patients and 13/24 haloperidol patients had a change of QT_c ≥ 30msec. After the second injection 18/25 ziprasidone patients and 14/24 haloperidol patients had a change of QT_c ≥ 30msec, with 1 ziprasidone patient with a change QT_c ≥ 60msec.

Heart rate increased with ziprasidone (7.8 and 12.1 beats/min at the C_{max}) and with haloperidol (2.5 and 5.9 beats/min).

Dose Response Studies

No relationship between QT_c change and IM ziprasidone dose was seen across doses of 2 mg to 20 mg in fixed-ziprasidone-dose trials previously. As above QT_c increased with a combination of larger and repeated dose.

Summary of Pharmacodynamics

- The comparator doses of haloperidol – two doses giving 17.5mg/day is greater than the maximum of 10mg/day set in efficacy studies (97-001, 050) and in practice lesser amounts (mean up to 7.7mg/day) were used in those studies. The doses of ziprasidone in this study – two doses giving 50mg/day is also greater than the amount actually used in those studies (mean up to 26.9mg/day), thus on a proportional basis the haloperidol dose was slightly greater than twice the mean effective dose and that of ziprasidone slightly less than twice.
- There was little difference in seen changes in QT_c between the groups in this Study.
- As a comparator dose for the effects on QT 10mg of parenteral haloperidol is the upper limit of the initial dose in the PI that may be repeated half hourly to a maximum of 100mg daily, i.e. much greater effects on QT might occur with haloperidol on this basis. However Martindale gives 2-10 mg for acute psychosis with subsequent doses hourly to a maximum of 18mg daily with an initial dose of 18mg for emergency in severely disturbed patients.
- The choice of 17.5 mg daily of haloperidol for comparison would thus appear reasonable in Study 063 which, although a PD study was essentially safety driven.

Thus on each drug, the patients had similar QT_c changes but received more than the recommended maximum daily dose of ziprasidone, compared with haloperidol at either the recommended maximum daily dose (Martindale) or much less than the recommended maximum daily dose (Aust. PI).

- The choice of 17.5 mg daily of haloperidol for comparison would thus appear reasonable in Study 063 which, although a PD study was essentially safety driven.

Thus on each drug, the patients had similar QT_c changes but received more than the recommended maximum daily dose of ziprasidone, compared with haloperidol at either the recommended maximum daily dose (Martindale) or much less than the recommended maximum daily dose (Aust. PI).

Efficacy

Pivotal Efficacy Studies

The original submission contained 2 separate studies (128 – 125 & 126) that were double-blind with the comparator 2mg ziprasidone mesilate, rather than placebo.

Other Efficacy and/or Safety Studies

Studies provided with this submission are summarised in Table 2.

Table 2. Non-pivotal efficacy studies

Design; Location; Population	Treatments; Dose, Duration; Subjects	Efficacy measures/outcomes	Efficacy results	Safety
<p>ZIP-NY-97-001</p> <p>Randomised multicentre, single blind parallel group flexible-dose study of the comparative efficacy, safety and tolerability of ziprasidone IM/PO vs. haloperidol IM/PO in patients with schizophrenia or schizoaffective disorder.</p> <p>Randomised 572, treated 429 Zip/138 Hal, completed 292/91.</p> <p>Zip: M/F 286/143</p> <p>Mean age: 34.0y (range 18-67)</p> <p>Hal: M/F 91/47</p> <p>Mean age 34.6y (range 17-65).</p>	<p>Ziprasidone IM/PO</p> <p>IM for 1-3 days: 10-20 mg, total \geq 40 mg during first 24 hours followed by</p> <p>PO: Initial 40 mg BD, adjusted to 40- 80 mg BD.</p> <p>Haloperidol IM/PO</p> <p>IM for 1-3 days: 2.5-5 mg, total \geq 10 mg during first 24h followed by</p> <p>PO: Initial 5mg BD, adjusted to 5-20 mg BD</p>	<p>Primary Efficacy Measures: change from baseline in Brief Psychiatric Rating Scale and the Clinical Global Impression-Severity, and the CGI-Improvement.</p> <p>Secondary Endpoints: Drug Attitude Inventory, Patient Preference Scale, Intensity of Care Questionnaire, and record of hospitalization and length of stay in high-dependency unit, Covi scale was added as a secondary endpoint</p>	<p>At End of IM Phase (Visit 1), the 95% CIs for the treatment difference in BPRS Total (ziprasidone minus haloperidol) were (-3.27, -0.76) (P = 0.0018). Predefined equivalence margin was 4 points</p> <p>Other IM phase parameters did not have this margin predefined.</p> <p>At End of IM Phase, the 95% CI for the treatment difference (ziprasidone minus haloperidol) in CGI-S was (-0.21, 0.03, P = 0.13).</p> <p>The CGI-I responder rates at End of IM Phase were, 56% for ziprasidone subjects vs. 51% for haloperidol The one-sided 95% confidence limit for the treatment difference (ziprasidone minus haloperidol) was -2.8%.</p>	<p>181 patients (126 - 29.4% vs. 55 - 39.9%) had \geq 1 AE in IM phase.</p> <p>1 Zip. related SAE on day 3 – schizophrenia worsening,</p> <p>26 (17 vs. 9) severe AEs.</p> <p>8 discontinuations (4 vs. 4) due to AEs, and 6 patients (5 vs. 1) had dose reductions or temporary discontinuation of study drug during the IM phase.</p> <p>Some of the subscales of the ESRS show statistical significance for ziprasidone at the end of the IM phase, but not the Barnes Akathisia Score.</p>
<p>A128105</p> <p>Randomised multicentre, single blind parallel group flexible-dose study of the comparative efficacy, safety and tolerability of ziprasidone IM/PO vs. haloperidol IM/PO in mostly Asian patients with schizophrenia or schizoaffective</p>	<p>Ziprasidone IM/PO</p> <p>IM for 1-3 days: 10-20 mg, total \geq 40 mg during first 24 hours followed by</p> <p>PO: Initial 40 mg BD, adjusted to 40- 80 mg BD</p> <p>Haloperidol IM/PO</p> <p>IM for 1-3 days:</p>	<p>Primary Efficacy Measures: change from baseline in Brief Psychiatric Rating Scale and the Clinical Global Impression-Severity, and the CGI-Improvement.</p> <p>Secondary Endpoints: Covi scale, Drug Attitude Inventory, Patient Preference Scale, Intensity of Care Questionnaire,</p>	<p>This was a non-inferiority study reassessed after unblinding as an equivalence study</p> <p>At End of IM Phase (Visit 1), the 95% CIs for the treatment difference in BPRS Total (ziprasidone minus haloperidol) were (-3.86, 0.13, P = 0.0664). Predefined non-inferiority margin was 4</p>	<p>93 patients (44 – 33.8% vs. 49 – 40.2%) had \geq 1 AE in IM phase. No SAEs.</p> <p>8 haloperidol (vs. 0) had a severe AE.</p> <p>10 discontinuations (5 vs. 5) due to AEs, and 8 patients (4 vs. 4) had dose reductions or temporary discontinuation of study drug during the</p>

Design; Location; Population	Treatments; Dose, Duration; Subjects	Efficacy measures/outcomes	Efficacy results	Safety
disorder. Randomised 256, treated 130 Zip/122 Hal, completed 107/103. Zip: M/F 93/37Mean age: 32.5y (range 18- 55)Hal: M/F 71/51 Mean age 32.8y (range 17-63).	2.5-5 mg, total \geq 10 mg during first 24h followed by PO: Initial 5mg BD, adjusted to 5-20 mg BD	and record of hospitalization and length of stay in high- dependency unit.	points	IM phase. The Barnes Akathisia Score and most of the subscales of the ESRS show statistical significance for ziprasidone at the end of the IM phase.

Study ZIPNY-97-001 Ziprasidone Intramuscular/Oral versus Haloperidol Intramuscular/Oral in the Treatment of Acute Exacerbation of Schizophrenia and Schizoaffective Disorder: a Six Week Open Administration Study with Blinded Assessments. 76 centres from 20 countries (including UK and Australia) recruited at least one screening or treated patient.

The primary objective of this study was to evaluate the comparative efficacy of IM/Oral ziprasidone versus haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder. The secondary objective was to assess safety and tolerability efficacy of IM/Oral ziprasidone versus haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder. The anxiolytic effect of ziprasidone versus haloperidol was also compared.

It was a multi-centre, parallel group comparison of efficacy and safety in acutely agitated patients with schizophrenia or schizoaffective disorder between IM ziprasidone and IM haloperidol administered for 1-3 days, followed by oral ziprasidone and haloperidol for a total treatment duration of 6 weeks. Study drug administration was open, with all assessments performed by raters blind to the patients' treatment allocation. There were differences in volume of the two drugs. Patients were randomized 3:1 to ziprasidone intramuscular/oral or haloperidol intramuscular/oral.

The primary measures of efficacy were the change from baseline in both the Brief Psychiatric Rating Scale (BPRS)⁴ and the Clinical Global Impression-Severity (CGI-S)⁵, and the CGI-Improvement (CGI-I).⁶

⁴ **The Brief Psychiatric Rating Scale (BPRS)** Total consists of 18 items (in italics below) from the Positive and Negative Symptom Scale (PANSS). The Positive and Negative Symptom Scales (PANSS) consist of three scales: positive scale, negative scale and general psychopathology scale. The scale consists of symptom constructs, each to be rated on a 7-point scale of severity (1 = absent or "best", 7 = extreme or "worst").

Positive Scale - Delusions, *Conceptual Disorganization, Hallucinatory Behaviour, Excitement, Grandiosity, Suspiciousness* Persecution, *Hostility*.

Negative Scale *Blunted Affect, Emotional Withdrawal, Poor Rapport, Social Withdrawal/ Apathy, Difficulty In Abstract Thinking, Lack Of Spontaneity And Flow Of Conversation, Stereotyped Thinking.*

General Psychopathology Scale *Somatic Concern, Anxiety, Guilt Feelings, Tension, Mannerism And Posturing, Depression, Motor Retardation, Uncooperative, Unusual Thought Content, Disorientation, Poor Attention, Lack Of Judgment And Insight, Disturbance Of Volition, Poor Impulse Control, Preoccupation, Active Social Avoidance.*

BPRS Total Score is the sum of ratings for all 18 items. The possible total scores are from 18 to 126.

⁵ **Clinical Global Impression Scale (CGI)** CGI is a scale used to assess any gross effects of any treatment on psychosis in all psychiatric patients with major disorders. Clinical Global Impression (CGI) scale consists of the

The secondary endpoints were Drug Attitude Inventory⁷, the Patient Preference Scale⁸, the Intensity of Care Questionnaire⁹, and the record of hospitalization (during the year)

Inclusion criteria were:

- Patients met DSM-IV criteria for schizophrenia or schizoaffective disorder.
- Patients entering hospital (or inpatients transferring to a higher-dependency unit) within the previous seven days because of acute exacerbation of psychotic symptoms.
- Patients with a minimum score of 40 on the BPRS scale (1-7).

Exclusion criteria were:

- Patients receiving an investigational agent in the previous six months.
- Concurrent treatment with antipsychotic agents at randomization (within 12 hours prior to randomization); for depot agents a period of two weeks or one cycle, whichever is the longer, must occur between last administration and randomization.
- Treatment with antidepressants or mood stabilizers within seven days of randomization; for MAOIs and moclobemide this period must be two weeks; for fluoxetine five weeks.
- Resistance to conventional drugs. (Resistance defined as failure to experience a therapeutic response during acute exacerbation following adequate trials of marketed antipsychotic agents on two or more occasions during the two years prior to study entry).
- Patients currently receiving clozapine (previous use of clozapine must have been at least 3 months prior to screening, and patients could not fit the criteria specified for treatment resistant).

Primary efficacy results were:

BPRS Total Score: At end of IM Phase (Visit 1), the 95% CIs for the treatment difference in BPRS Total (ziprasidone minus haloperidol) was (-3.27, -0.76, P = 0.0018).

severity scale (CGI-S) and the global improvement scale (CGI-I). CGI severity score possible values: 0 = Not assessed, 1 = Normal, not at all ill, 2 = Borderline mentally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among the most extremely ill patients.

⁶ **CGI Improvement score** possible values 0 = Not assessed, 1 = Very much improved, 2 = Much improved, 3 = Improved, 4 = No change, 5 = Worse, 6 = Much worse, 7 = Very much worse.

⁷ **Drug Attitude Inventory (DAI)** is a 30-item self-report inventory of the subjective effects of neuroleptic medications in-patients with schizophrenia. It is designed to measure schizophrenia patients' subjective responses to medications as well as values and attitudes toward illness and health. The answers are scored positive or negative, the final score being the total number of positive scores minus the negative scores, i.e. a possible range of + 30 to - 30. A positive total final score means a positive subjective response (compliant). A negative total score means a negative subjective response (non-compliant).

⁸ **Patient Preference Scale** a subjective 1 to 5 scale in answer to "What is your opinion of your current medication?" at the baseline and Compared to the previous medicine (tablets or injection) your doctor has prescribed for your condition, how does this current medication compare?" at subsequent visits.

⁹ **Intensity of Care Questionnaire** This comprises a record of the previous (24h) requirement level of nursing care from 1 = minimal to 5 = continuous and an opinion on the level of care currently required (rated 1 to 3).

CGI-S: At End of IM Phase (Visit 1), the 95% CI for the treatment difference (ziprasidone minus haloperidol) in CGI-S was (-0.21, 0.03, P = 0.13). This CI crossed zero and remained within 0.25 points or less – *which was not a pre defined margin*.

CGI-I Scores: For CGI-I, the primary inference analyses were based on the response status of the final CGI-I score (1, 2 or 3). The responder rates at End of IM Phase were, respectively, 56% for ziprasidone subjects versus 51% for haloperidol. The one-sided 95% CI for the treatment difference (ziprasidone minus haloperidol) was -2.8%. Non-inferiority between the two treatment groups at End of IM Phase was claimed for CGI-I responder rates.

Study A1281050 Ziprasidone Intramuscular/Oral versus Haloperidol Intramuscular/Oral in the Treatment of Acute Exacerbation of Schizophrenia and Schizoaffective Disorder: a Six Week Open Administration Study with Blinded Assessments.

This study was essentially the same as Study ZIPNY-97-001 the differences being in the inclusion of the Covi scale¹⁰ in the secondary outcomes prior to commencement of the study and the statistical approach to the study. It was conducted in 21 centres in 7 countries including Hong Kong, Malaysia and Singapore. Objectives, design, duration, study type, comparator groups and endpoints, inclusion and exclusion criteria were all the same as ZIPNY-97-001. This study was defined as a non-inferiority study, unlike Study 97-001 which was an equivalence (“comparable”) study. The non-inferiority (equivalence) margin was 4 points in the BPRS scale (a difference of < 4 points in reduction from baseline was not considered clinically meaningful).

Primary efficacy results were:

BPRS Total Score: At End of IM Phase (Visit 1), the 95% CIs for the treatment difference in BPRS Total (ziprasidone minus haloperidol) were (-3.43, 2.43, P = 0.7385).

CGI-S: At End of IM Phase (Visit 1), the 95% CIs for the treatment difference (ziprasidone minus haloperidol) in CGI-S were (-0.15, 0.15, P = 0.9880) The confidence interval crossed zero and remained within 0.25 points or less – *which was not a pre defined margin*.

CGI-I Scores: For CGI-I, the primary inference analyses were based on the response status of the final CGI-I score (1, 2 or 3).

The responder rates at End of IM Phase were, respectively, 56% for ziprasidone subjects versus 51% for haloperidol. The two-sided 90% CI for the treatment difference (ziprasidone minus haloperidol) was -6.8%, 13.6%. Comparability between the two treatment groups at End of IM Phase was claimed for CGI-I responder rates.

Summary of Efficacy

The 2 separate studies (128 – 125 & 126) that were contained in the original submission were assessed by the previous Delegate as:

- The studies showed that both 10mg and 20mg of ziprasidone IM were statistically significantly superior to 2mg of ziprasidone IM in reducing agitation as measured by the primary efficacy endpoint of the AUC of BAS over 0-2 hours (for 10mg) and 0-4 hours (for 20mg). However, only the 20mg dose was statistically significantly superior to the 2mg dose in reducing agitation

¹⁰ **COVI Scale** This evaluates speech, behaviour, and the somatic complaints of anxiety (each is evaluated 0-4 with 0 = absent i.e. total score range is 0 to 12 with ≥ 6 indicates the presence of anxiety and ≤ 3 corresponds to mild or absent). This was used to monitor anxiolytic effect of the study drug. Generally ≤ 3 is regarded as a success while > 3 is regarded as a treatment failure. As defined in the studies here the Covi scale assesses anxiety based on 1-5 scoring of 3 items – verbal report, behaviour and somatic signs for a score of 3-15 – essentially the same scales.

as measured by the primary efficacy endpoint of CGI-S. There were a number of secondary efficacy endpoints and neither 10mg nor 20mg IM achieved statistically significant superiority over 2mg IM for all of these.

- Patient numbers exposed to the two proposed doses of ziprasidone IM in the two pivotal studies were low (n=102), and patient numbers for conditions other than schizophrenia and schizoaffective disorder were negligible.
- It is considered that both study [#125] and study [#126] are primarily dose ranging rather than pivotal for efficacy.

With the further studies in this submission, efficacy at the proposed dose has been adequately demonstrated. In this submission there are 2 efficacy studies essentially similar in design, the difference being in the statistical approach to the study. Study 97-001 was an equivalence (“comparable”) study, unlike Study A1281050 which was defined as a non-inferiority study.

Study 001 shows equivalence for IM ziprasidone mesilate on the basis of BPRS Total Score. The study also claims equivalence or non-inferiority on both the other two primary endpoints as well as several secondary ones but on the basis of endpoints that were not predefined.

The daily dose of ziprasidone was approximately 20mg (21.3 ± 6.8) while for haloperidol it was approximately 7mg (7.1 ± 2.7), both given as 2 injections daily.

Both studies included only patients with schizophrenia and schizoaffective disorder.

The studies added a further 413 patients with schizophrenia and 48 with schizoaffective disorder who received ziprasidone mesilate.

Study 050 started as a non-inferiority study with 90% CIs, but after the results were received it was reinterpreted as an equivalence study with mostly 95% CIs. The reason given for this was to enable the study report to be comparable to that of the companion trial.

Also in this submission were published reports of two previously submitted trials (128-121 and 128-306) and one trial (97-001) that was part of this submission.

- The tolerability of intramuscular ziprasidone and haloperidol treatment and the transition to oral therapy. Daniel et al. *International Clinical Psychopharmacology* 2004, Vol 19 No 1 (study 128-121).

This article did not add relevant new data:

Because this was an exploratory study of tolerability and safety, no formal statistical analyses were included in the protocol. The scope for symptom improvement with IM treatment was limited because of the relatively modest levels of psychopathology upon entry.

- Intramuscular Ziprasidone Compared With Intramuscular Haloperidol in the Treatment of Acute Psychosis. Brook et al. *J Clin Psychiatry* 61:12, December 2 (study 128-306).

This article gave some new data (presumably post-hoc) in its statistical interpretation of efficacy results claiming ziprasidone mesilate was statistically significantly more effective (p-values only were calculated).

The need to obtain written informed consent, essential for this evaluation of an experimental treatment, excluded severely psychotic, very hostile, confused, and disorganized patients from entering the study. However, the patients in the present study had sufficiently high levels of baseline psychopathology to enable demonstration of clinically meaningful treatment effects.

Safety

Renal effects

In the original submission, the evaluator noted that the major pre-clinical issue relates to the clinical relevance of the renal toxicity of the excipient SBECD seen in animals. The sponsor's response to the clinical relevance of the renal toxicity was to refer to the absence of renal AEs in the studies.

In the current submission the sponsor argues for the safety of the excipient SBECD on the basis of TGA approval of its use with voriconazole, however the PI for that drug states:

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), including dialysis patients, accumulation of the intravenous vehicle SBECD occurs. Oral voriconazole should not be administered to these patients unless an assessment of the risk to the patient justifies the use of intravenous voriconazole.

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

New data provided on SBECD included Study A1501016: An open, parallel group multi-centre study to determine the effects of impaired renal function on the pharmacokinetics, safety and toleration of SBECD following multiple dosing with the IV formulation.

It showed in the moderate renal impairment subjects, SBECD peak plasma concentrations, AUC, and elimination half-lives were increased due to decreased clearance. There was a strong correlation between SBECD clearance and creatinine clearance.

These studies, after 3 days exposure, showed no incidence of abnormality in creatinine or BUN (Study 046 0/19 and Study 121 0/200). There was a very low incidence of abnormality after 24 h exposure in studies in this submission (Study 001 - Creatinine 1/381, BUN 1/381; Study 050 - Creatinine 1/125; Study 063 0/5).

The studies in this submission added an additional 584 patients exposed to ziprasidone mesilate.

Pivotal studies

No new data.

Other studies

Study 063

There were 2 discontinuations due to study drug in each group, those for ziprasidone were EPS (extrapyramidal symptoms); hypotension and dizziness felt to be an interaction with valsartan. 29/31 on ziprasidone and 25/27 on haloperidol had at least 1 AE (Table 3). All were mild or moderate except for 1 severe EPS on haloperidol.

There were 29/31 treatment emergent AEs on ziprasidone and 24/27 on haloperidol. Routine study laboratory results were only available in 8 patients were comparable at baseline in the two treatment groups. Changes systolic and diastolic blood pressure and pulse rate were small and variable.

Table 3 Study 063 Treatment-related AEs (Incidence \geq 5%)

Body System Event	Ziprasidone		Haloperidol	
	(No. of Subjects: Severity)	%	(No. of Subjects: Severity)	%
Nervous System				
Agitation	2 mild	6.5	3 mild	11.1
Anxiety	2 mild, 1 mod	9.7	1 mild	3.7
Dizziness	5 mild, 1 mod	19.4	2 mild	7.4
EPS	1 mild, 1 mod	6.5	6 mild, 2 mod, 1 severe	33.3
Somnolence	18 mild, 10 mod	90.3	17 mild, 5 mod	81.5
Digestive System				
Nausea	2 mild, 1 mod	9.7	2 mild	7.4
Dry Mouth	4 mild	12.9	2 mild	7.4
Body as a Whole				
Injection site pain	2 mild	6.5	1 mild	3.7
Malaise	1 mild, 1 mod	6.5	1 mild	3.7
Skin & Appendages				
Sweating	--	0	2 mild	7.4

Study 001

429 ziprasidone and 138 haloperidol patients were in the safety population. Of these, 181 patients (126 - 29.4% ziprasidone vs. 55 - 39.9% haloperidol) experienced one or more AEs during the IM phase (Table 4). There was 1 study drug related SAE on day 3 – schizophrenia worsening, that because of the timing may have been related to IM ziprasidone rather than oral drug.

Twenty six patients (17 vs. 9) had a severe AE. Eight patients (4 vs. 4) were discontinued from treatment due to AEs, and 6 patients (5 vs. 1) had dose reductions or temporary discontinuation of study drug during the IM phase.

Some of the subscales of the ESRS show statistical significance for ziprasidone at the end of the IM phase, but not the Barnes Akathisia Score.

Table 4 Study 001 Incidence and severity of most frequent (\geq 5%) treatment-emergent AEs

Subjects evaluable for AEs Body system and COSTART Preferred term	Ziprasidone (N = 429)					Haloperidol (N = 138)				
	No	(%)	Severity*			No	(%)	Severity*		
			Mild	Mod.	Sev			Mild	Mod.	Sev
NERVOUS SYSTEM										
Akathisia	6	(1.4)	2	2	2	12	(8.7)	6	5	1
Dystonia	6	(1.4)	0	2	4	11	(8.0)	3	6	2
Extrapyramidal Symptoms	4	(0.9)	3	1	0	15	(10.9)	6	6	3
Hypertonia	7	(1.6)	2	4	1	13	(9.4)	4	8	1
Insomnia	28	(6.5)	13	13	2	7	(5.1)	2	4	1

Study 050

130 ziprasidone and 122 haloperidol patients were in the safety population. Of these, 93 patients (44 – 33.8% vs. 49 – 40.2%) experienced one or more AEs during the IM phase (Table 5). There were no SAEs. Eight patients on haloperidol (vs. 0) had a severe AE. 10 patients (5 vs. 5) were discontinued from treatment due to AEs, and 8 patients (4 vs. 4) had dose reductions or temporary discontinuation of study drug during the IM phase.

The Barnes Akathisia Score and most of the subscales of the ESRS show statistical significance for ziprasidone at the end of the IM phase.

Elevated Prolactin levels were of higher incidence in haloperidol treated patients in both studies but the time course was not indicated.

Table 5 Study 050 Incidence and severity of most frequent ($\geq 5\%$) treatment-emergent AEs.

Subjects evaluable for AEs Body system and COSTART Preferred term	Ziprasidone (N = 429)					Haloperidol (N = 138)				
	No	(%)	Severity*			No	(%)	Severity*		
			Mild	Mod.	Sev			Mild	Mod.	Sev
DIGESTIVE SYSTEM										
Nausea	8	(6.2)	5	3	0	2	(1.6)	1	1	0
NERVOUS SYSTEM										
Akathisia	2	(1.5)	1	1	0	7	(5.7)	2	2	3
Dystonia	12	(9.2)	10	2	0	4	(3.3)	3	1	0
Extrapyramidal Symptoms	6	(4.6)	4	2	0	27	(22.1)	4	17	6
Insomnia	3	(2.3)	3	0	0	7	(5.7)	4	3	0
Somnolence	8	(6.2)	7	1	0	4	(3.3)	2	2	0

Deaths and Other Serious Adverse Events

There were no relevant deaths, and one SAE of schizophrenia worsening on ziprasidone mesilate in this submission.

Post-market Safety Data

The only data with this submission related to a search for renal failure – of 54 cases, 14 treatment route unknown, only 3 were from IM ziprasidone mesilate, all of whom showed prior signs of renal deterioration.

Safety Summary and Conclusions

While QT_C prolongation appears to be unlikely to be a problem when used in accordance with the proposed regimen, and while renal effects for ziprasidone mesilate could not be shown, there is the accumulation of SBECD seen in Study A1501016.

Clinical Summary and Conclusions

This submission has addressed the lack of data on C_{max} values after repeated IM administration, likewise the lack of data on the metabolism of ziprasidone when given IM. Ziprasidone has been proposed to be given at doses of up to 40 mg daily for up to 3 consecutive days in patients, not specifically excluding those already taking oral ziprasidone or other neuroleptic medication. PK data from study 063 support use for up to 24 hours. It is notable that the mean C_{max} for

ziprasidone after the second dose was 319 ng/mL while the C_{max} after the maximum oral dose of 80 mg bd is 202 ng/mL (as cited in the FDA scientific review of ziprasidone IM, 6 June 2002). The PK of continuing doses, particularly the effect of increasing levels of M9 which has a t_{1/2} of over 20 hours has not been examined. This is of particular concern given that ziprasidone, M9 and M10 when tested *in vitro* share properties which may predict a QTc prolonging effect. However data from safety and efficacy studies including those where high, multiple doses were given suggest that QTc prolongation from ziprasidone IM at the proposed dose regimen is comparable to that which occurs with therapeutic use of haloperidol IM. The results of the population PK analysis were as expected for a drug that is primarily metabolised in the liver. Given that the analysis did not include data from subjects / patients with hepatic or renal impairment it does not provide assurance for use in these groups.

With the further studies in this submission, efficacy at the proposed dose has been adequately demonstrated. In this submission there are 2 efficacy studies essentially similar in design, the difference being in the statistical approach to the study. Study 97-001 was an equivalence (“comparable”) study, unlike Study A1281050 which was defined as a non-inferiority study.

While QT_C prolongation appears to be unlikely to be a problem when used in accordance with the proposed regimen, and while renal effects for ziprasidone mesilate could not be shown, there is the accumulation of SBECD seen in Study A1501016.

V. Pharmacovigilance Findings

No pharmacovigilance data were provided.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the Delegate’s overview and recommendation.

Quality

There were no pharmaceutical chemistry objections to the initial submission to register Zeldox IM. No significant pharmaceutical chemistry changes have been made to the drug substance or to the manufacture and specifications of the product. The specification for the excipient, SBECD, has been amended and the limit for the genotoxic impurity 1,4-butane sultone has been amended, making exposure to this compound at the maximum daily dose of Zeldox IM below the limit of toxicological concern.

The level of 1,4-butane sultone increases during storage of the product. The sponsor has agreed to an acceptable limit 1,4-butane sultone and a shelf-life of 2 years at below 30°C.

Non-Clinical

There were no nonclinical objections to the original submission for registration of Zeldox IM and no subsequent nonclinical objections following review of additional nonclinical data. There had been some concern about nephrotoxicity of the excipient SBECD. SBECD has shown renal toxicity in repeat dose nonclinical studies at exposures ~ double the clinical exposure at the maximum recommended human dose.

SBECD is present as an excipient in voriconazole (Vfend) with respective clinical SBECD approximately 8-fold higher than that proposed for Zeldox IM.

SBECD also contains an impurity, 1,4-butane sultone, a mutagen and rodent carcinogen which should be controlled. This limit has subsequently revised.

Results of local tolerance studies suggest that if multiple injections are required clinically then they should be given at different sites.

Clinical

Three new clinical studies and a population PK report were submitted.

Patients with significant hepatic or renal impairment were not enrolled in the studies included in this population PK analysis. These data and data from study 063 alone suggest that ziprasidone at the doses proposed results in a similar QTc prolongation to haloperidol given at comparative therapeutic doses.

Two new double-blind, active comparator-controlled, rater-blinded safety and efficacy studies were submitted. The primary efficacy measure was change from baseline in the Brief Psychiatric Rating Scale (BPRS) and in the Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scales. Non-inferiority was claimed if the upper limit of the CI for change from baseline in BPRS was < 4 points. This difference was considered to be not clinically meaningful. A non-inferiority margin was not specified a priori for CGI-S and CGI-I. For CGI-I “responders” were those patients with a score of 1, 2 or 3 (equating to very much improved to improved on a 1 to 7 point scale where 1 = very much improved and 7 = very much worse) at the end of the IM treatment period. At the end of the IM treatment period in the first study, mean change from baseline BPRS was -6.139 for ziprasidone and -4.150 for haloperidol (95% CI for difference -3.25, -0.73), demonstrating superiority of ziprasidone with haloperidol. Responder rates (for CGI-I) were 56% for ziprasidone and 51% for haloperidol (95% CI for difference -2.8, 13.3%), demonstrating comparability of ziprasidone and haloperidol. In the second study, non-inferiority of ziprasidone vs. haloperidol was demonstrated for BPRS and responder rates. The 95% CI for between treatment difference in change from baseline BPRS at the end of the IM treatment period was (-3.86, 0.13). Responder rates were comparable at 62% for ziprasidone and 58% for haloperidol (95% CI for difference -6.8%, 13.6%).

The excipient SBECD was associated with renal toxicity in rats and dogs and previous ADEC discussions had noted that the renal safety of ziprasidone IM had not been adequately investigated. Renal function data from the previously submitted high dose studies (046 and 121) where up to 20 mg ziprasidone was given via IMI for 3 days were also presented in this submission and no clinically significant acute effects on renal function were apparent. Renal function was also assessed in the newly submitted studies and no clinically significant changes were apparent. New data concerning SBECD were available from study A1501016, which was evaluated in relation to submission 99/2441/2 to register Vfend (voriconazole) which is also sponsored by the sponsor. 96 mg/kg SBECD was infused for 2 doses at 12 hour intervals on day 1 followed by 48 mg/kg at 12 hour intervals on days 2 to 7. That study demonstrated that SBECD peak plasma concentrations, AUC and $t_{1/2}$ were increased in patients with moderate renal impairment (CLcr 30-50 mL/min). Clearance of SBECD was reduced approximately 50%.

No new safety issues were identified in the additional data contained in this submission.

Risk-Benefit Analysis

The clinical evaluator recommended the initially proposed indication be amended such that “*rapid control*” and replaced with “*acute control*”. This is a more appropriate expression for the intended use and was supported by the Delegate. The sponsor agreed with the change. The Delegate also argued that the initially proposed statement that *If indicated, the patient may continue with oral ziprasidone* is not relevant to use of Zeldox IM and could be considered promotional and it should not be included in the indication. The Delegate considered it unnecessary and suggested it could be replaced with a statement to the effect that Zeldox IM should be used when oral therapy is not appropriate. This would be consistent with the wording in the indications for olanzapine (Zyprexa IM). Use should also be restricted to patients with agitation due to schizophrenia and related psychoses, not to all patients with psychotic disorders as is currently proposed, as efficacy has been demonstrated only in patients with schizophrenia or schizoaffective psychosis.

Ziprasidone has been proposed to be given at doses of up to 40 mg daily for up to 3 consecutive days in patients, not specifically excluding those already taking oral ziprasidone or other neuroleptic medication. PK data from study 063 support use for up to 24 hours. It is notable that the mean

C_{max} for ziprasidone after the second dose was 319 ng/mL while the C_{max} after the maximum oral dose of 80 mg bd is 202 ng/mL (as cited in the FDA scientific review of ziprasidone IM, 6 June 2002). The PK of continuing doses, particularly the effect of increasing levels of M9 which has a t_{1/2} of over 20 hours has not been examined. This is of particular concern given that ziprasidone, M9 and M10 when tested *in vitro* share properties which may predict a QTc prolonging effect. However data from safety and efficacy studies including those where high, multiple doses were given suggest that QTc prolongation from ziprasidone IM at the proposed dose regimen is comparable to that which occurs with therapeutic use of haloperidol IM.

The results of the population PK analysis were as expected for a drug that is primarily metabolised in the liver. Given that the analysis did not include data from subjects / patients with hepatic or renal impairment it does not provide assurance for use in these groups.

The maximum recommended dose of haloperidol is 100 mg daily by IM or IVI which is much higher than is likely to be used and significantly less than the dose given in studies 063, 001 and 050. The dose of haloperidol used in the pivotal studies is acceptable and these studies demonstrated satisfactory efficacy of ziprasidone IMI for up to 3 days using the proposed dose regimen.

The safety issues previously of concern were renal safety and QTc prolongation with multiple dosing. These issues have now been addressed. Each vial of Zeldox IM contains 441.49 mg SBECD compared with 3200 mg per vial of voriconazole, which also contains this substance. The maximum daily exposure to SBECD with Zeldox IM would be 883mg. This suggests accumulation is unlikely to occur in patients with moderate renal impairment when given as proposed. SBECD is haemodialysed with clearance of 55 mL/minute (from the voriconazole PI). Zeldox IM prolongs QTc interval to a similar extent as haloperidol.

There remains a lack of PK data on patients stabilised on oral ziprasidone who were treated with IM ziprasidone subsequent to becoming agitated.

In previously submitted data the most commonly occurring treatment-related adverse events in patients receiving ziprasidone IM 5-20 mg were dizziness (11.6%), nausea (10.3%), somnolence (9.4%) and pain at the injection site (8.7%). All of these adverse events occurred more frequently with ziprasidone than with haloperidol, but movement disorders occurred more frequently with haloperidol than with ziprasidone.

The Delegate proposed to register Zeldox IM (ziprasidone mesilate) 20 mg/ mL powder for injection for *acute control and short term management of agitation and disturbed behaviours in patients with schizophrenia and related psychoses when oral therapy is not appropriate*.

The advice of the Australian Drug Evaluation Committee (ADEC) was requested, particularly with regard to use in patients currently taking neuroleptic medication. Having considered the evaluations and the Delegate's overview, the ADEC agreed with the Delegate that there is a lack of data on the use of intramuscular ziprasidone in patients currently taking oral ziprasidone, but considered this can be addressed by inclusion in the Product Information of a statement similar to that in the US package insert, viz "since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended."

ADEC recommended approval of the application with the indication proposed by the Delegate.

Outcome

Based on review of quality, safety and efficacy data, TGA approved the registration of Zeldox IM, ziprasidone (as mesilate) 20mg/ml powder for injection vial with diluent, indicated for:

Acute treatment and short term management of agitation and disturbed behaviour in patients with schizophrenia and related psychoses when oral therapy is not appropriate.

Attachment 1. Product Information

PRODUCT INFORMATION

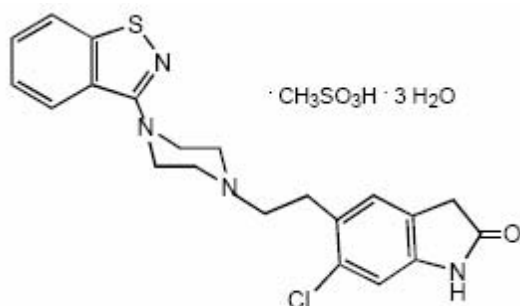
ZELDOX IM

(ziprasidone mesilate)

DESCRIPTION

Ziprasidone is an antipsychotic agent chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. Ziprasidone free base has a molecular weight of 412.94. Ziprasidone mesilate has a molecular weight of 563.09, with the following chemical name:

5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate. Australian Approved Names: Ziprasidone (C₂₁H₂₁ClN₄OS) and Ziprasidone mesilate (C₂₁H₂₁ClN₄OS.CH₃SO₃H.3H₂O). The CAS Registry Numbers are CAS-146939-27-7 ziprasidone, and CAS-185021-64-1 ziprasidone mesilate. The empirical formula of C₂₁H₂₁ClN₄OS.CH₃SO₃H.3H₂O represents the following structural formula:



Ziprasidone is a white to slightly pink powder. Ziprasidone mesilate is slightly soluble in methanol (5.0mg/mL) and water (1.1mg/mL) and practically insoluble in tetrahydrofuran (0.09mg/mL). The solubility of ziprasidone mesilate in 30% (w/v) sulfobutyl betadex sodium (SBECD) was determined to be 45mg/mL.

Zeldox IM is presented as a sterile lyophilised powder in a single dose vial as ziprasidone mesilate containing the equivalent of 30mg ziprasidone. When reconstituted with 1.2mL of Water for Injections, each mL contains 20mg of ziprasidone and 294mg of the inactive ingredient, sulfobutyl betadex sodium (SBECD).

PHARMACOLOGY

Pharmacodynamics

Receptor Binding Studies

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D₂ and D₃, 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 H₁ receptor (K_i= 47 nM).

Ziprasidone functioned as an antagonist at the D₂, 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 (IC₅₀ >1 μM).

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 (5HT₂) antagonism.

Antagonism at receptors other than dopamine and 5HT₂ 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.

Receptor Functional Studies

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A (5HT_{2A}) and dopamine type 2 (D₂) 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.

Positron Emission Tomography Studies

Receptor blockade, 12 hours after a single oral dose of 40mg, was greater than 80% for 5HT_{2A} and greater than 50% for D₂ using positron emission tomography (PET).

Pharmacokinetics

Absorption

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.

Distribution

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.

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 DRUG INTERACTIONS).

After ziprasidone is administered intramuscularly, approximately 20% of the dose is excreted in urine and approximately 66% is eliminated in faeces.

Elimination

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

The mean terminal half life on the third day of dosing ranged from 8 to 10 hours. The mean terminal half-life of ziprasidone after intravenous administration is 3 hours. Mean clearance of ziprasidone administered intravenously is 5mL/min/kg.

The mean terminal half life of ziprasidone after intramuscular administration of single doses ranges from 2 to 5 hours.

Special Populations

Age and Gender

No clinically significant age- or gender-differences in the pharmacokinetics were observed following oral administration.

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 oral ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking

Pharmacokinetic screening of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

Hepatic Impairment

In mild to moderate impairment of liver function (Child Pugh A or B) caused by cirrhosis, the serum concentrations after oral administration were 30% higher and the terminal half-life was about two hours longer than in normal patients.

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 oral ziprasidone following 8 days of 20mg 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 oral ziprasidone have been observed in patients with decreased kidney function (creatinine clearance <10mL/min).

It is unknown whether serum concentrations of the metabolites are increased in these patients.

As SBECD is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

CLINICAL TRIALS

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.

The results for the BPRS from these two studies are presented in the table below; responders were those patients with a Clinical Global Impression - Improvement (CGI-I) score of 1, 2 or 3 (equates to very much improved to improved).

	Study 1		Study 2	
	End IM Phase	End IM/Oral Phase	End IM Phase	End IM/Oral Phase
Change from baseline – total BPRS score (ziprasidone vs. haloperidol)	-6.15 vs. -4.13 p=0.0018	-	-7.73 vs. -5.86 p=0.0664	-
95% CI treatment difference – total BPRS score	-3.27, -0.76	-1.86, 3.47 p=0.55	-3.86, 0.13	-3.43, 2.43 p=0.7385
Responder rates	56% ziprasidone 51% haloperidol p=0.4866	74% ziprasidone 75% haloperidol p=0.4840	62% ziprasidone 58% haloperidol p=0.5353	78% ziprasidone 76% haloperidol p=0.5948

Ziprasidone was superior to haloperidol (LOCF on the ITT Analysis Set) in the change from baseline in the total BPRS score at the end of the IM phase in the first study and comparable to haloperidol in the second study. Ziprasidone was also comparable to haloperidol with respect to responder rates at both the end of the IM and the end of the IM/oral phase in both studies.

INDICATIONS

Acute treatment and short term management of agitation and disturbed behaviour in patients with schizophrenia and related psychoses when oral therapy is not appropriate.

CONTRAINDICATIONS

Known hypersensitivity to any ingredient of the product.

Recent acute myocardial infarction.

Uncompensated heart failure.

Conditions with a potential to increase QT interval:

- QT-interval prolongation or history of QT prolongation
- Congenital long QT syndrome
- Use with other drugs known to increase the QT interval

- Arrhythmias treated with Class IA and III antiarrhythmic drugs (see PRECAUTIONS).

PRECAUTIONS

QT Prolongation and Pro-arrhythmias

Ziprasidone causes a mild to moderate prolongation of the QT interval.

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was coadministered with the appropriate inhibitor(s) of the CYP450 metabolism specific for each drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for oral ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of oral ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200mg twice daily).

In placebo-controlled schizophrenia trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160mg. In schizophrenia clinical trials with ziprasidone, the electrocardiograms of 3/3266 (0.1%) patients who received ziprasidone and 1/538 (0.2%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone.

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20mg then 30mg) or haloperidol (7.5mg then 10mg) given four hours apart. Note that a 30mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

Some drugs including Class IA and III antiarrhythmics that prolong the QT/QTc interval greater than 500 msec have been associated with the occurrence of torsade de pointes and with sudden unexplained death.

There have been rare post-marketing reports of torsade de pointes in patients with multiple confounding risk factors taking ziprasidone. A causal relationship with ziprasidone has not been established.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. Experience with ziprasidone has not revealed an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalaemia or hypomagnesaemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval (see CONTRAINDICATIONS).

If cardiac symptoms such as palpitations, vertigo, syncope or seizures occur, then the possibility of a malignant cardiac arrhythmia should be considered and a cardiac evaluation including an ECG should be performed. If the QTc interval is >500 msec, then it is recommended that the treatment should be stopped (see CONTRAINDICATIONS).

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalaemia in particular, have baseline serum potassium and magnesium measurements. Hypokalaemia may result from diuretic therapy, diarrhoea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness (see CONTRAINDICATIONS). Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome, a potentially fatal complex, has been reported in association with antipsychotic drugs, including ziprasidone. The clinical manifestations are hyperthermia, muscle rigidity, altered mental status and signs of autonomic instability such as irregular pulse and blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional features may include elevated creatine phosphokinase, rhabdomyolysis and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ziprasidone, should be discontinued.

Tardive Dyskinesia

In fixed-dose, placebo-controlled trials, in patients with schizophrenia, of up to six weeks duration, the incidence of treatment emergent tardive dyskinesia was comparable in patients receiving oral ziprasidone and placebo and lower than patients treated with active comparator (0.4% ziprasidone, 1.2% haloperidol and 0.7% placebo). In a 52-week, placebo-controlled trial in patients with schizophrenia, only one out of 219 patients treated with oral ziprasidone experienced tardive dyskinesia.

As with other antipsychotic agents, the risk of tardive dyskinesia and other tardive extrapyramidal syndromes may increase with long term exposure and therefore if signs or symptoms of tardive dyskinesia appear in a patient on ziprasidone, a dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Cardiovascular Disease

Patients with cardiovascular disease have not been included in clinical trials in sufficient numbers. Thus, the safe use of the intramuscular product has not been established (see CONTRAINDICATIONS).

Blood Pressure

Dizziness, tachycardia and postural hypotension are not unusual in patients following intramuscular administration of ziprasidone. Single cases of hypertension have also been reported. Caution should be exercised, particularly in ambulatory patients.

Oral ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1 -adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with oral ziprasidone in schizophrenia clinical trials.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease or conditions which would predispose patients to hypotension.

CNS Drugs and Alcohol

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting agents, including alcohol and drugs acting on the dopaminergic and serotonergic systems.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycaemia or diabetes in patients treated with ziprasidone. Although

fewer patients have been treated with ziprasidone, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia related adverse events is not completely understood. However, epidemiological studies, which did not include ziprasidone, suggest an increased risk of treatment emergent hyperglycaemia related adverse events in patients treated with atypical antipsychotics included in these studies. Because ziprasidone was not marketed at the time these studies were performed, it is not known if ziprasidone is associated with this increased risk. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued, however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Rash

In premarketing schizophrenia trials with oral ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of oral ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Hyperprolactinemia

As with other drugs that antagonise dopamine D₂ receptors, oral ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see Carcinogenicity). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to

date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Seizures

As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared with placebo. Analyses of seventeen oral placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Ziprasidone is not approved for the treatment of elderly patients with dementia-related psychosis.

Carcinogenicity, Genotoxicity, Effects on Fertility

Carcinogenicity

Lifetime carcinogenicity studies were conducted with ziprasidone hydrochloride administered in the diet to rats and mice. In rats, there was no evidence of increased tumour incidences at doses up to 12mg/kg/day, corresponding to systemic exposure (plasma AUC_{0-24 h}) similar to that in humans at the maximum recommended dose. In male mice, there was no increase in tumour incidences at doses up to 200mg/kg/day, corresponding to systemic exposure about 2.5 times that in humans. In female mice, dose-related increases in the incidence of hyperplasia and neoplasia in the pituitary (shown immunohistochemically to be prolactin-producing) and mammary gland were seen at 50 to 200mg/kg/day, corresponding to systemic exposure about 1 to 4 times greater than that in humans; a no-effect dose level for these effects was not established. Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are associated with increased prolactin concentrations. Although clinical and epidemiological studies have not shown an association between chronic administration of this class of drugs and tumourigenesis in humans, the use of ziprasidone in patients with familial history or previously detected breast cancer should be avoided. Caution should be exercised when considering ziprasidone treatment in patients with pituitary tumours.

Genotoxicity

Ziprasidone hydrochloride was tested for genotoxic potential in assays for gene mutation and chromosomal damage. There was a reproducible response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Equivocal results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes. Ziprasidone hydrochloride was negative in *in vivo* chromosomal aberration assay in mouse bone marrow.

Effects on Fertility

Ziprasidone hydrochloride was shown to increase time to copulation in rats at oral doses of 10 to 160mg/kg/day (0.5 to 8 times the oral MRHD on a mg/m² basis). Fertility was impaired in rats dosed orally with ziprasidone hydrochloride 160mg/kg/day, with a no-effect dose level of 40mg/kg/day (2 times the MRHD on a mg/m² basis). The effect appeared to be in the female since the length of the oestrous cycle was increased, a pharmacologic effect of dopamine antagonists in rats. Increased oestrous cycle length was observed in female rats treated intramuscularly with ziprasidone mesilate 2mg/kg/day or greater (less than the clinical exposure based on AUC). Fertility was not impaired when males were given oral ziprasidone hydrochloride 160mg/kg/day or intramuscular ziprasidone mesilate 20mg/kg/day (6 times the clinical exposure based on AUC) and mated with untreated females, and there were no treatment related findings in the testes of male rats given ziprasidone hydrochloride 200mg/kg/day orally (11 times the MRHD on a mg/m² basis).

Use in Pregnancy

Category B3

In animal studies ziprasidone hydrochloride crossed the placenta and demonstrated developmental toxicity, including possible teratogenic effects at doses/exposures similar to clinical doses/exposures. When ziprasidone hydrochloride was administered to pregnant rabbits during the period of organogenesis, there was an increased incidence of foetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) at an oral dose of 30mg/kg/day (3 times the MRHD on a mg/m² basis), and an increased incidence of vertebral arches fused to the pelvis after intramuscular ziprasidone mesilate at 5mg/kg/day or greater (twice the clinical exposure based on AUC). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect doses were 10mg/kg/day orally (similar to the MHRD on a mg/m² basis) and 1mg/kg/day intramuscular ziprasidone mesilate (less than clinical exposure based on AUC). Studies in rats have not shown adverse effects on embryo-foetal development, other than those associated with maternal toxicity, when ziprasidone hydrochloride was administered during the period of organogenesis at oral doses up to 160mg/kg/day (8 times the MRHD on a mg/m² basis) or intramuscular ziprasidone mesilate up to 40mg/kg/day (11-fold the clinical exposure based on AUC).

The incidence of still births was increased when ziprasidone was administered at oral doses of ziprasidone hydrochloride of 10mg/kg/day or greater to rats throughout gestation or intramuscular doses of ziprasidone mesilate of 2mg/kg/day or greater. Estimated systemic exposure at the no-effect dose for perinatal mortality (5mg/kg/day or 2mg/kg/day for oral and intramuscular administration, respectively) was less than that in humans at the maximum recommended dose. Offspring showed increased postnatal mortality, suppression of growth and delayed development when ziprasidone was administered to rats orally during gestation and lactation at 40mg/kg/day (2 times the MRHD on a mg/m² basis) or intramuscularly at 6mg/kg/day or greater (2 times the clinical exposure based on AUC). The estimated systemic exposure in dams at the no-effect dose for offspring (5mg/kg/day orally or 2mg/kg/day intramuscularly) was less than that in humans at the MHRD.

There are no adequate and well controlled clinical trials in pregnant women. As human experience is limited, administration of ziprasidone is not recommended during pregnancy.

Ziprasidone should be used in pregnancy only if needed and if the expected benefit to the mother outweighs the potential risk to the foetus.

Use in Lactation

It is not known whether ziprasidone is excreted in animal or human milk. Offspring showed increased postnatal mortality, suppression of growth and delayed development when ziprasidone was administered to rats orally during gestation and lactation at 40mg/kg/day (2 times the MRHD on a mg/m² basis) or intramuscularly at 6mg/kg/day or greater (2 times the clinical exposure based on AUC). The estimated systemic exposure in dams at the no-effect dose for offspring (5mg/kg/day orally or 2mg/kg/day intramuscularly) was less than that in humans at the MHRD. Patients should be advised not to breast feed an infant if they are taking ziprasidone.

Use in Children

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

Use in the Elderly

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Use in Renal Impairment

As SBECD is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function (see Pharmacokinetics).

Use in Hepatic Impairment

In mild to moderate impairment of liver function (Child Pugh A or B) caused by cirrhoses, the serum concentrations after oral administration were 30% higher and the terminal half-life was about two hours longer than in normal patients.

In patients with mild to moderate hepatic insufficiency, lower doses should be considered.

A toxicity study in dogs showed intrahepatic cholestasis and elevation of serum ALT and alkaline phosphatase at oral ziprasidone doses producing exposure (plasma AUC) about twice the maximal clinical exposure.

There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group (see Pharmacokinetics).

DRUG INTERACTIONS

All interaction studies have been conducted with oral ziprasidone.

Effect of Ziprasidone on Other Drugs

Using human liver microsomes, ziprasidone demonstrated no inhibitory effect on CYP1A2, CYP2C9 or CYP2C19. The concentration of ziprasidone required to inhibit CYP2D6 and CYP3A4 *in vitro* is at least 1000 fold higher than the free concentration that can be expected *in vivo*. Although the clinical relevance of this finding is uncertain, ziprasidone is unlikely to cause clinically important drug interactions mediated by these enzymes.

QTc Prolongation

As with other antipsychotic agents, there is an increased potential of QTc prolongation in the presence of Type IA and IIIA antiarrhythmics. Coadministration with the potent CYP3A4 inhibitor, ketoconazole, did not affect QTc, when compared to ziprasidone alone (see CONTRAINDICATIONS).

Dextromethorphan

The pharmacokinetics and metabolism of dextromethorphan, a CYP2D6 substrate were unaffected by ziprasidone.

Oral Contraceptives

Ziprasidone administration at a dose of 20mg twice daily resulted in no significant change to the pharmacokinetics of oestrogen (ethinyl oestradiol 0.03mg, a CYP3A4 substrate) or progesterone components (levonorgesterol 0.15mg).

Lithium

Co-administration of ziprasidone at a dose of 40mg twice daily had no effect on pharmacokinetics of lithium at a dose of 450mg twice daily for 7 days. In this study, steady state lithium concentrations prior to coadministration of ziprasidone were 0.49 mEq/L.

As ziprasidone and lithium are associated with cardiac conduction changes, the combination may pose a potential for pharmacodynamic interaction, including arrhythmias. While there have been no reports of clinically significant QTc increases in clinical trials of adjunctive therapy involving ziprasidone and lithium, caution should be exercised in prescribing the two drugs together.

Protein Binding

Ziprasidone extensively binds to plasma proteins. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is unlikely.

Effects of Other Drugs on Ziprasidone

Coadministration of potent CYP3A4 inhibitors has the potential of increasing ziprasidone serum concentrations. The clinical importance of this potential has not been clearly defined.

Ketoconazole

A potent CYP3A4 inhibitor (400mg/day), increased the serum concentrations of ziprasidone by approximately 35-40% when compared to ziprasidone alone. The serum concentration of S-methyl-dihydroziprasidone, at the expected T_{max} of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.

Carbamazepine

A CYP3A4 inducer, produced a decrease in AUC (36%) and C_{max} (25%) of ziprasidone.

Cimetidine

A CYP3A4 inhibitor, at a dose of 800mg QD for 2 days did not significantly alter the pharmacokinetics of ziprasidone.

CNS Drugs

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. As it exhibits *in vitro* dopamine antagonism, ziprasidone may antagonise the effects of direct and indirect dopamine agonists.

Antacid

Multiple doses of aluminium and magnesium containing antacid did not affect the pharmacokinetics of ziprasidone.

Other

In addition, pharmacokinetic screening of patients in clinical trials has not revealed any evidence of clinically significant interactions with benztropine, propranolol or lorazepam.

Ziprasidone has not been studied for drug interaction with valproate or lamotrigine.

Effects on Ability to Drive and Use of Machines

As with other psychoactive drugs, ziprasidone may cause somnolence. Patients likely to drive or operate other machines should therefore be cautioned appropriately.

ADVERSE EFFECTS

Ziprasidone Intramuscular

The table below contains adverse events with possible, probable or unknown relationship to ziprasidone in phase 2/3 trials. The most common reactions were nausea, sedation, dizziness, injection site pain, headache and somnolence.

All adverse reactions are listed by class and frequency (very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)).

The adverse reactions listed below may also be associated with the underlying disease and/or concomitant medications.

Body System	Adverse Drug Reactions
Metabolism and nutrition disorders	
Uncommon	Anorexia
Psychiatric disorders	
Uncommon	Agitation, antisocial behaviour, psychotic disorder, insomnia, tic, anxiety
Nervous system disorders	
Common	Akathisia, dizziness, dystonia, headache, sedation, somnolence
Uncommon	Cogwheel rigidity, dizziness postural, dysarthria, dyskinesia, dyspraxia, parkinsonism, tremor
Cardiac disorders	
Uncommon	Bradycardia, tachycardia
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Common	Hypertension
Uncommon	Flushing, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon	Laryngospasm
Gastrointestinal disorders	
Common	Nausea, vomiting
Uncommon	Constipation, diarrhoea, loose stools, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon	Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Common	Muscle rigidity
General disorders and administration site conditions	
Common	Asthenia, injection site burning, injection site pain
Uncommon	Drug withdrawal syndrome, fatigue, influenza like illness, injection site discomfort, injection site irritation
Investigations	
Uncommon	Blood pressure decreased, hepatic enzyme increased

The most common cardiovascular adverse events reported from fixed dose clinical trials with intramuscular ziprasidone were: dizziness (10mg - 11%, 20mg - 12%), tachycardia (10mg - 4%, 20mg - 4%) and postural dizziness (10mg - 2%, 20mg - 2%), orthostatic hypotension, 20mg - 5%) and hypotension (10mg - 2%).

In premarketing fixed dose clinical trials with ziprasidone intramuscular injection, increased blood pressure and hypertension were observed in 2.2% of patients receiving 10mg and increased blood pressure was observed in 2.8% of patients receiving 20mg.

The table below contains treatment-emergent, all causality adverse events with an incidence of $\geq 1\%$ for ziprasidone IM and haloperidol IM from two clinical studies.

Body System / Adverse Event	Percentage of Patients Reporting Events	
	Ziprasidone IM N=559	Haloperidol IM N=260
Body as a Whole		
Appl. / inj. / incision / insertion site pain	6 (1.07)	0 (0.00)
Asthenia	20 (3.58)	1 (0.38)
Headache	11 (1.97)	4 (1.54)
Digestive		
Constipation	2 (0.36)	3 (1.15)
Increased salivation	2 (0.36)	4 (1.54)
Nausea	15 (2.68)	3 (1.15)
Vomiting	13 (2.33)	2 (0.77)
Nervous		
Agitation	3 (0.54)	7 (2.69)
Akathisia	8 (1.43)	19 (7.31)
Anxiety	11 (1.97)	9 (3.46)
Dizziness	32 (5.72)	6 (2.31)
Dyskinesia	1 (0.18)	3 (1.15)
Dystonia	6 (1.07)	15 (5.77)
Extrapyramidal syndrome	10 (1.79)	42 (16.15)
Hypertonia	7 (1.25)	13 (5.00)
Insomnia	31 (5.55)	14 (5.38)
Somnolence	26 (4.65)	9 (3.46)
Tremor	4 (0.72)	3 (1.15)
Respiratory		
Respiratory tract infection	1 (0.18)	3 (1.15)
Special Senses		
Abnormal vision	1 (0.18)	3 (1.15)

Ziprasidone Oral

The table below contains treatment-emergent adverse events that occurred at an incidence of greater than or equal to 1% in monotherapy double-blind placebo-controlled studies in patients with bipolar mania and short-term double-blind, placebo-controlled studies in patients with schizophrenia.

Body System / Adverse Event	Percentage of Patients Reporting Events	
	Ziprasidone N = 1159	Placebo N = 497
General Disorders and Administration Site Conditions		
Asthenia	1.3	0.2
Fatigue	1.6	0.4
Eye Disorders		
Vision blurred	1.6	0.8
Gastrointestinal Disorders		
Constipation	2.7	2.0
Dry Mouth	2.5	1.4
Diarrhoea	0.9	1.0
Dyspepsia	1.7	0.6
Gastrointestinal discomfort	0.77	2.6
Nausea	4.0	3.0
Salivary hypersecretion	1.0	0.2
Tongue thick	1.4	0.2
Vomiting	2.2	1.2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal stiffness	1.8	0.4
Nervous System Disorders		
Akathisia	8.7	4.8
Dizziness	6.2	3.2
Dyskinesia	1.2	0.6
Dystonia	4.5	1.2
Extrapyramidal disorder	5.7	1.8
Headache	5.3	4.8
Parkinsonism	1.2	0.4
Sedation	9.2	2.6
Somnolence	4.7	1.2
Tremor	2.5	1.6
Psychiatric Disorders		
Restlessness	1.6	0.6
Insomnia	1.2	2.4

The following adverse events occurred in placebo-controlled clinical trials at an incidence of less than 1% and greater than placebo.

All adverse reactions are listed by class and frequency: very common (>10%), common (1% to 10%), uncommon (0.1% to 1%) and rare (<0.1%).

General Disorders and Administration Site Conditions - *Uncommon*: Gait abnormal, thirst. *Rare*: Chest pain, feeling hot, pyrexia, sluggishness.

Cardiac Disorders - *Uncommon*: Bundle branch block right, palpitation.

Gastrointestinal Disorders - *Uncommon*: Dysphagia, flatulence, gastritis. *Rare*: Gastro-oesophageal reflux, loose stools.

Blood and Lymphatic System Disorders - *Rare*: Lymphopenia.

Ear and Labyrinth Disorders - *Uncommon*: Tinnitus. *Rare*: Ear pain, vertigo positional.

Eye Disorders - *Uncommon*: Photophobia. *Rare*: Amblyopia, eye pruritus, visual disturbance.

Investigations - *Uncommon*: Hepatic enzyme increased, increased appetite, heart rate increased. *Rare*: Blood lactic dehydrogenase increased, body temperature increased, electrocardiogram QT corrected interval prolonged, eosinophil count increased, eosinophil count abnormal, hypocalcaemia, liver function test abnormal, pulse increased.

Infections and Infestations - *Uncommon*: Rhinitis.

Musculoskeletal and Connective Tissue Disorders - *Uncommon*: Joint stiffness, muscle cramps, pain in extremity. *Rare*: Arthropathy, musculoskeletal discomfort, trismus.

Nervous System Disorders - *Uncommon*: Ataxia, bradykinesia, cogwheel rigidity, disturbance in attention, dizziness postural, drooling, dysarthria, generalised tonic-clonic seizures, hypokinesia, hypersomnia, hypoaesthesia, lethargy, oculogyric crisis, paraesthesia, tardive dyskinesia, vertigo. *Rare*: Akinesia, hypertonia, paresis, restless legs syndrome, torticollis.

Psychiatric Disorders - *Uncommon*: Agitation, anxiety, throat tightness, nightmare; *Rare*: Anorgasmia, bradyphrenia, flat affect, panic attack, sleep walking.

Respiratory, Thoracic and Mediastinal Disorders - *Uncommon*: Dyspnoea, sore throat. *Rare*: Hiccups.

Renal and Urinary Disorders - *Uncommon*: Dysuria, urinary incontinence.

Reproductive System and Breast Disorders - *Rare*: Erectile dysfunction, erection increased, galactorrhoea, gynaecomastia.

Skin and Subcutaneous Tissue - *Uncommon*: Acne, maculopapular rash, rash, urticaria. *Rare*: Alopecia, dermatitis allergic, erythema, psoriasis, skin irritation, swelling face, rash papular.

Other Findings for Ziprasidone Oral

Extrapyramidal Symptoms (EPS)

In double-blind active controlled clinical trials in patients with schizophrenia, the Movement Disorder Burden Scale, a composite measure of EPS, was statistically significantly ($p < 0.05$) in favour of ziprasidone versus haloperidol and risperidone. In addition the reported incidence of akathisia and use of anticholinergic drugs was greater in the haloperidol and risperidone groups relative to ziprasidone. The incidence of reported EPS for ziprasidone-treated patients in the short-term, placebo-controlled trials was 5% vs. 1% for placebo.

Body Weight

The incidence of body-weight gain, recorded as an adverse event in short-term 4- and 6-week, fixed-dose, placebo-controlled schizophrenia trials, was low and identical in

ziprasidone-treated and placebo-treated patients (both 0.4%). There was a small increase in median weight in ziprasidone-treated patients (0.5kg) but not in placebo-treated patients.

In a one-year placebo-controlled schizophrenia study a median weight loss of 1-3kg was observed in ziprasidone-treated patients compared to a 3kg median loss in placebo-treated patients.

QT Interval

In schizophrenia clinical trials with oral ziprasidone, an increase of 30 to 60 msec was seen in 12.3% (976/7941) of ECG tracings from ziprasidone-treated and 7.5% (83/975) of ECG tracings from placebo-treated patients. A prolongation of >60 msec was seen in 1.6% (128/7941) and 1.2% (12/975) of tracings from ziprasidone and placebo-treated patients, respectively. The incidence of QTc interval prolongation above 500 msec was 3 in a total of 3266 (0.1%) in ziprasidone treated patients and 1 in a total of 538 (0.2%) in placebo treated patients.

Dose Dependency of Adverse Events in Short-term, Placebo-Controlled Trials

An analysis for dose response in this 4-study pool revealed an apparent relation of adverse event to dose for the following events: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Vital Sign Changes

Ziprasidone is associated with orthostatic hypotension (see PRECAUTIONS).

Prolactin Levels

There were only transient prolactin increases seen during chronic dosing with ziprasidone.

In phase 2/3 clinical trials, prolactin levels in patients treated with ziprasidone were sometimes elevated (12%) compared with the placebo group (3%), but potential clinical manifestation (e.g. gynaecomastia 0.1%) were rare. In most patients, levels returned to normal ranges without cessation of treatment. In the clinical studies the degree and incidence of prolactin elevation was lower in ziprasidone patients than in patients treated with haloperidol (29%) or risperidone (60%).

Physical and Psychological Dependence

Ziprasidone has not been systemically studied in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g. development of tolerance, increases in dose, drug seeking behaviour).

Post-Marketing Experience

The following adverse events have been reported during oral ziprasidone post-marketing experience and have not been listed above:

Immune system disorders: Allergic reaction

Psychiatric Disorders: Mania/hypomania

Nervous System Disorders: Facial droop, neuroleptic malignant syndrome (see Precautions); serotonin syndrome (alone or in combination with serotonergic medicinal products)

Cardiac Disorders: Tachycardia, torsade de pointes (see Precautions)

Vascular Disorders: Postural hypotension, syncope

Gastrointestinal Disorders: Dysphagia

Skin and Subcutaneous Tissue Disorders: Angioedema

Renal and Urinary Disorders: Enuresis

Reproductive System and Breast Disorders: Priapism

DOSAGE AND ADMINISTRATION

For intramuscular use only. Do not administer intravenously.

Intravenous administration must be avoided.

The recommended dose is 10 to 20mg administered as required up to a maximum dose of 40mg per day. Doses of 10mg may be administered every 2 hours, doses of 20mg may be administered every 4 hours up to a maximum of 40mg/day.

Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If therapy is indicated, oral ziprasidone hydrochloride capsules, up to 80mg twice daily, should replace the intramuscular administration as soon as possible.

Use in Renal Impairment

As SBECD is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function (see Pharmacokinetics).

Use in Hepatic Impairment

In mild to moderate impairment of liver function (Child Pugh A or B) caused by cirrhoses, the serum concentrations after oral administration were 30% higher and the terminal half-life was about two hours longer than in normal patients.

In patients with mild to moderate hepatic insufficiency, lower doses should be considered.

A toxicity study in dogs showed intrahepatic cholestasis and elevation of serum ALT and alkaline phosphatase at oral ziprasidone doses producing exposure (plasma AUC) about twice the maximal clinical exposure.

There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group (see Pharmacokinetics).

Use in the Elderly

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Effects of Smoking

No dosage adjustment is required in patients who smoke (see Pharmacokinetics – Metabolism).

Preparation for Administration

Zeldox IM should only be administered by intramuscular injection. This product is for single use in one patient only. Vials require reconstitution prior to administration, any unused portion should be discarded.

Add 1.2mL of the supplied Sterile Water for Injections to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20mg ziprasidone. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injections.

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, store at 2-8°C (Refrigerate. Do not freeze) for not more than 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Due to the viscosity of the solution, approximately 0.5mL of the reconstituted solution remains in the vial following administration.

OVERDOSAGE

Experience with oral ziprasidone in overdose is limited. In overdose cases in general, the most commonly reported symptoms are extrapyramidal symptoms, somnolence, tremor and anxiety. Hypertension, hypotension, diarrhea, tachycardia and prolongation of the QTc and QRS intervals have also been reported. Respiratory depression may occur following massive overdoses due to CNS depression. The largest confirmed single ingestion is 12,800mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae) were reported.

In cases of suspected overdose, the possibility of multiple drug involvement should be considered. There is no specific antidote to ziprasidone. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation and oxygenation. Monitor respiratory function, vital signs and blood pressure. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, adrenaline and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Monitor for CNS depression, seizures and extrapyramidal reactions. In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Monitor liver function tests as increased serum liver enzymes may result following overdose.

The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis, therefore emesis is not recommended. Administration of activated charcoal should be considered and is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Given the high protein binding of ziprasidone haemodialysis is unlikely to be beneficial in the treatment of overdose. Close medical monitoring and supervision should continue until the patient recovers.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

Zeldox IM for intramuscular injection is presented as a sterile lyophilised powder in a single dose vial as ziprasidone mesilate containing the equivalent of 30mg ziprasidone. When reconstituted, each mL contains 20mg of ziprasidone (see DOSAGE AND ADMINISTRATION – Preparation for Administration).

An ampoule containing 1.2mL of Sterile Water for Injections Ph. Eur. is also supplied for reconstitution purposes.

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, store at 2-8°C (Refrigerate. Do not freeze) for not more than 24 hours.

Store below 30°C in dry form. Do not freeze.

Keep vials in the original pack until ready to use.

Poison schedule: S4

NAME AND ADDRESS OF SPONSOR

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