ZELDOX® IM
(Ziprasidone Mesilate)

1. NAME OF THE MEDICINAL PRODUCT

ZELDOX® IM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ziprasidone mesilate, equivalent to 20 mg of ziprasidone per mL, following reconstitution.

3. PHARMACEUTICAL FORM

Powder for solution for intramuscular injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Rapid control of agitation in psychotic patients.[1]

A dose-related reduction in agitated behavior was observed with onset of significant improvement noted at 15 minutes and then from 1 hour post-injection until end point (2 hours) with the 10 mg dose and from 30 minutes post-injection until endpoint (4 hours) with the 20 mg dose.[3,4]

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Ziprasidone IM is for intramuscular use only. Do not administer intravenously.[89]

Use in adults

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every 4 hours up to a maximum of 40 mg/day.[5]

Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.[6,7,8]

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as clinically appropriate.[6,7,8]

Use in children

Safety and effectiveness in children under 18 years have not been established.

Use in the elderly

Safety and effectiveness in the elderly (65 years and over) have not been established.[9]

Use in renal impairment

Since the cyclodextrin excipient in ziprasidone intramuscular injection is excreted exclusively by the kidney, it should be administered with caution in patients with impaired renal function.[10] (See section **5.2. – Pharmacokinetic properties**)

Use in hepatic impairment

In patients with mild to moderate hepatic insufficiency, lower doses should be considered. There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group.[11] (See section **5.2. – Pharmacokinetic properties**)

Use in smokers

No dosage adjustment is required in patients who smoke.[12]

4.3. CONTRAINDICATIONS

Ziprasidone is contraindicated in patients with:

- Known hypersensitivity to ziprasidone or any of the excipients;
- Known QT interval prolongation including congenital long QT Syndrome;[13]
- Recent myocardial infarction;[13]
- Uncompensated heart failure;[13]
- Cardiac arrhythmias requiring treatment with Class IA and III antiarrhythmic drugs.[13] (See section **4.4. – Special warnings and precautions for use**)

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

QT interval

Ziprasidone causes a mild to moderate prolongation of the QT interval.[14]

In the pre-marketing clinical trials database for the oral formulation, the incidence of QTc 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.[15,62] One in 541 (0.18%) patients receiving intramuscular ziprasidone had QTc prolongation (≥500 msec).[16]

Some drugs including Class IA and III antiarrhythmics that prolong the QT interval have been associated with the rare occurrence of *torsade de pointes*, a life-threatening arrhythmia.[17] (See section **4.3. - Contraindications**)

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.[72]

Ziprasidone should be used with caution in patients with the following risk factors, which can increase the risk for occurrence of this arrhythmia:

- bradycardia
- electrolyte imbalance
- concomitant use with other drugs that prolong QT.[17]

If cardiac symptoms suggestive of arrhythmias are observed or reported during treatment, then appropriate cardiac diagnostics should be performed. If the QTc interval is greater than 500 msec, it is recommended that treatment be stopped. (See section **4.3. - Contraindications**)

Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs, since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ziprasidone and preventive measures undertaken.[94]

Neuroleptic malignant syndrome (NMS)

NMS, a potentially fatal complex, has been reported in association with antipsychotic drugs, including ziprasidone.[71,73] 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 must be discontinued.

Severe Cutaneous Adverse Reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with ziprasidone exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.[97,98]

Other severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported with ziprasidone exposure.

Severe cutaneous adverse reactions are sometimes fatal. Discontinue ziprasidone if severe cutaneous adverse reactions occur.[97]

Tardive dyskinesia

There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.[19]

Falls

Antipsychotic drugs (which includes ziprasidone) may cause somnolence, postural hypotension, and motor and sensory instability, which could lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, a fall risk assessment should be completed when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.[101]

Cardiovascular disease

Safety and effectiveness in patients with cardiovascular disease have not been established.[20]

Blood pressure

Dizziness, tachycardia, hypertension and postural hypotension may occur in patients following intramuscular administration of ziprasidone. Caution should be exercised, particularly in ambulatory patients.[21]

Seizures

Caution is recommended when treating patients with a history of seizures.

CNS drugs/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.[22]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis have been shown to be at an increased risk of death and/or potentially, cerebrovascular adverse events compared with placebo when treated with some antipsychotic drugs.[86,87,101] Study data with ziprasidone in the treatment of elderly patients with dementia are insufficient to conclude whether or not there is an increased risk of death with ziprasidone versus placebo in this patient population. Ziprasidone is not approved for the treatment of elderly patients with dementia-related psychosis.[76]

Post-marketing Reports of Mortality

As with other IM antipsychotics, fatalities with the use of ziprasidone IM, generally in patients with multiple confounding risk factors, have been reported. Although a causal relationship has not been established, ziprasidone IM should be used with caution.[91]

Priapism

Cases of priapism have been reported with antipsychotic use, including ziprasidone. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.[92]

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Class IA and III Antiarrhythmic Drugs. (See sections **4.3 - Contraindications** and **4.4 – Special warnings and precautions for use** - QT interval.)

Concomitant Use with Other Drugs that Prolong QT Interval. (See section **4.4 – Special warnings and precautions for use -** QT interval.)

CNS Drugs/Alcohol. (See section **4.4 – Special warnings and precautions for use** CNS drugs/alcohol.)

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.[23] 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*.[82,83,84]

Dextromethorphan – Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the CYP2D6 mediated metabolism of dextromethorphan to its major metabolite, dextrorphan.[24]

Oral Contraceptives – Ziprasidone administration results in no significant change to the pharmacokinetics of estrogen (ethinyl estradiol, a CYP3A4 substrate) or progesterone components.[25]

Lithium – Co-administration of ziprasidone has no effect on the pharmacokinetics of lithium.[26]

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.[27,28,29]

Effects of other drugs on ziprasidone

In vitro data animal data suggest that ziprasidone may be a P-glycoprotein (P-gp) substrate. The *in vivo* relevance for humans remains unknown.

Ketoconazole 400 mg/day, a potent inhibitor of CYP3A4, which also inhibits P-gp, produced an increase of approximately 35% in ziprasidone exposure (AUC and C_{max}).[31] Since ziprasidone is a substrate of CYP3A4 and induction of CYP3A4 and P-gp is related, co-administration with inducers of CYP-3A4 and P-gp such as carbamazepine, rifampin and St. John´s Wort could cause decreased concentrations of ziprasidone.[94,99] Carbamazepine 200 mg twice daily, an inducer of CYP3A4, produced a decrease of 36% in ziprasidone exposure.[32,99]

Cimetidine, a nonspecific CYP inhibitor, did not significantly affect ziprasidone pharmacokinetics.[33]

4.6. FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy

No studies have been conducted in pregnant women. Women of child-bearing potential receiving ziprasidone should therefore be advised to use an appropriate method of contraception. As human experience is limited, administration of ziprasidone is not recommended during pregnancy unless the expected benefit to the mother outweighs the potential risk to the fetus.[41] (See section **5.3. - Preclinical safety data**)

Use in lactation

There are no adequate and well-controlled studies in lactating women. Limited data indicate that ziprasidone is excreted into breast milk at very low levels. Patients should be advised not to breastfeed if they are receiving ziprasidone.[42,102]

Fertility

There are no adequate and well-controlled studies in women and men exposed to ziprasidone.

Contraception – Women of childbearing potential receiving ziprasidone should be advised to use an appropriate method of contraception.[101]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ziprasidone may cause somnolence. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ziprasidone does not affect them adversely.

4.8. UNDESIRABLE EFFECTS

Adverse drug reactions reported from clinical trials and post-marketing experience include:

Adverse Drug Reaction Table[100]

System Organ Class	**Adverse Drug Reactions**
Immune system disorders	Hypersensitivity[71]*
Metabolism and nutrition disorders	Decreased appetite
Psychiatric disorders	Mania[77*], Hypomania[77*], Psychotic disorder , Agitation, Insomnia[66*]
Nervous system disorders	Neuroleptic malignant syndrome[71*], Serotonin syndrome[78*a], Tardive dyskinesia[85*], Syncope[79*], Dystonia[88*], Extrapyramidal disorder, Dyskinesia, Cogwheel rigidity, Akathisia, Tremor, Somnolence, Headache, Dizziness, Facial droop[85*]
Ear and labyrinth disorders	Vertigo
Cardiac disorders	*Torsade de* pointes[72*b], Tachycardia[65*], Bradycardia
Vascular disorders	Embolism venous[94*b†], Orthostatic hypotension[63*], Hypertension, Hypotension[91*], Hot flush
Respiratory, thoracic and mediastinal disorders	Laryngospasm[D]
Gastrointestinal disorders	Dysphagia[85*], Vomiting[64*], Tongue oedema[85*†], Nausea, Constipation, Diarrhea, Dry mouth

Adverse Drug Reaction Table[100]

System Organ Class	Adverse Drug Reactions
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)[97*], Angioedema[80*], Rash[67*], Hyperhidrosis
Renal and urinary disorders	Dysuria, Urinary incontinence[85*], Enuresis[85*]
Reproductive system and breast disorders	Priapism[81*], Galactorrhoea[71,73*]
General disorders and administration site conditions	Asthenia, Injection site pain, Fatigue

*ADR identified post-marketing
†MedDRA updated
a. Alone or in combination with serotonergic medicinal products
b. See section **4.4. Special warnings and precautions for use**
D. Dystonic effect

4.9. OVERDOSE

There is no experience of overdosage with ziprasidone intramuscular injection.[43] Experience with ziprasidone capsules overdosage is limited. The largest confirmed single ingestion is 12,800 mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae) were reported.[74] In overdose cases in general; the most commonly reported symptoms are extrapyramidal symptoms, somnolence, tremor, and anxiety.[75]

There is no specific antidote to ziprasidone. In cases of acute overdosage, establish and maintain an airway and ensure adequate ventilation and oxygenation. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Given the high protein binding of ziprasidone, hemodialysis is unlikely to be beneficial in the treatment of overdose. Close medical monitoring and supervision should continue until the patient recovers.[46]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Receptor binding studies

Ziprasidone has a high affinity for dopamine type 2 (D_2) receptors and substantially higher affinity for serotonin type 2_A ($5HT_{2A}$) receptors. Ziprasidone also interacts with serotonin $5HT_{2C}$, $5HT_{1D}$ and $5HT_{1A}$ receptors where its affinities for these sites are equal to or greater than its affinity for the D_2 receptor. Ziprasidone has moderate affinity for neuronal serotonin and norepinephrine transporters. Ziprasidone demonstrates moderate affinity for histamine H_1- and $alpha_1$-receptors. Ziprasidone demonstrates negligible affinity for muscarinic M_1-receptors.[47]

Receptor functional studies

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A ($5HT_{2A}$) and dopamine type 2 (D_2) receptors.[48]

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.[48]

Human PET studies

At 12 hours following a 40 mg oral dose of ziprasidone, receptor blockade was greater than 80% for $5HT_{2A}$ and greater than 50% for D_2 using positron emission tomography (PET).[49]

Further Information from Clinical Trials

Results of a Large Post-Marketing Safety Study

A randomized post-approval study of 18,239 patients with observational follow-up for 1 year was conducted to determine whether ziprasidone's effect on the QTc interval is associated with an increased risk of non-suicide mortality in patients with schizophrenia. This study, which was conducted in naturalistic clinical practice settings, showed no difference in the rate of non-suicide mortality between ziprasidone and olanzapine treatments.[90]

5.2. PHARMACOKINETIC PROPERTIES

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 or earlier and the mean half-life ($t_{½}$) ranges from approximately two to five hours.[68,69,70] Exposure increases in a dose-related manner and, following three days of intramuscular dosing, little accumulation is observed.[50]

Mean systemic clearance of ziprasidone administered intravenously is 7.5 mL/min/kg and the volume of distribution is approximately 1.5 L/kg.[51]

Ziprasidone is extensively bound (>99%) to plasma proteins and its binding appears to be independent of concentration.[52]

Ziprasidone is extensively metabolized after oral administration, with only a small amount (<1%) excreted in urine or feces (<4%) as unchanged drug.[53]

Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyldihydroziprasidone. Approximately 20% of the dose is excreted in urine, with approximately 66% being eliminated in feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum.[54]

Ziprasidone is primarily metabolized by two pathways: reduction and methylation to generate S-methyldihydroziprasidone which accounts for approximately two-thirds of the metabolism, and oxidative metabolism accounting for the other third. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the first step is mediated primarily by chemical reduction by glutathione as well as by enzymatic

reduction by aldehyde oxidase. The second step is methylation mediated by thiol methyltransferase. *In vitro* studies indicate that CYP3A4 is the major cytochrome P450 catalyzing the oxidative metabolism of ziprasidone.[53,93]

Ziprasidone, S-methyldihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties, which may predict a QTc-prolonging effect. S-methyldihydroziprasidone is mainly eliminated by fecal excretion and CYP3A4 catalyzed metabolism. The sulphoxide is eliminated through renal extraction and by secondary metabolism catalyzed by CYP3A4.[54]

In a phase I trial, the CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of ziprasidone by <40%. The serum concentration of S-methyldihydroziprasidone, at the expected T_{max} of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.[55]

No clinically significant differences in the pharmacokinetics of ziprasidone in young and elderly, male or female subjects were observed following oral administration.[56]

Pharmacokinetic evaluation of ziprasidone serum concentrations of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.[57]

No marked differences in the pharmacokinetics of oral ziprasidone have been observed in patients with moderate to severe impairments in renal function as compared with subjects with normal renal clearance. It is unknown whether serum concentrations of the metabolites are increased in these patients.[58]

As the cyclodextrin excipient in ziprasidone intramuscular injection is cleared by renal filtration, ziprasidone should be administered with caution to patients with impaired renal function.[59]

In mild to moderate impairment of liver function (Child-Pugh A or B), the serum concentrations after oral administration were 30% higher and the terminal half-life was about two hours longer than in normal patients.[60]

5.3. PRECLINICAL SAFETY DATA

Preclinical safety data on ziprasidone administered orally revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. In reproductive studies in rats and rabbits, ziprasidone has shown no evidence of teratogenicity. Adverse effects on fertility and increased numbers of pups born dead, decreased pup weights and delayed functional development were observed at doses that caused maternal toxicity (e.g., sedation, decreased body weight gain). Increased perinatal mortality and delayed functional development of offspring occurred at maternal plasma concentrations extrapolated to be similar to the maximal concentrations in humans given therapeutic doses.[61]

In parenteral studies of ziprasidone there were no adverse findings relevant to the clinical use of the product.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sulphobutyl ether β-cyclodextrin sodium

6.2. INCOMPATIBILITIES

This medicinal product should only be mixed with Water for Injections. (See section **6.6 - Special precautions for disposal and other handling**)

6.3. SHELF LIFE

36 months

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours at 25°C and seven days at 2°C to 8°C. However from a microbiological point of view, immediate use after reconstitution or after 24 hours at 2°C to 8°C is recommended.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Storage and handling

Store below 30°C.

Keep vials in the original packaging until use.

Freezing should be avoided to prevent damage to the diluent ampule.

6.5. NATURE AND CONTENTS OF CONTAINER

Type I flint glass vials containing powder (ziprasidone mesylate) equivalent to 30 mg of ziprasidone. The vials are sealed with butyl rubber lyophile stoppers and flip-off aluminum seals.

Type I flint glass ampules containing 1.2 mL Water for Injections Ph. Eur.

Pack size: 1 vial and 1 ampule per carton.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The contents of the vial should be reconstituted by introduction of 1.2 mL of the supplied Water for Injections affording a concentration of 20 mg ziprasidone per mL, and shaken until complete dissolution has occurred. Only clear solutions, free of visible particles, should be used.

Only one dose should be withdrawn from each vial and the remainder should be discarded.

ZELDOX IM/LPD/PK-03
According to CDS V 18.0 dated 14-Sep-2018; Supersedes CDS V 17.0 dated 12-May-2018

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7. REFERENCES

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2. Paragraph deleted from section 4.1 (Therapeutic indications) per ziprasidone team when IPI was retired (22Sep06): In two one-week open-label, active-controlled trials, ziprasidone was administered by intramuscular injection for up to three days with patients subsequently continuing on oral ziprasidone. Maintenance of efficacy, safety and tolerability were demonstrated for the transition from intramuscular to oral administration of ziprasidone. – IM CER Section 4.2.5 Studies 128-121, 128-306.

3. FINAL STUDY REPORT: PROTOCOL 128-125 A Phase III Randomized Study Comparing 2 Doses of Intramuscular Ziprasidone (2 mg and 10 mg) in Subjects with Psychosis and Acute Agitation, dated 20 November 1997.

4. FINAL STUDY REPORT: PROTOCOL 128-126 A Phase III Randomized Study Comparing 2 Doses of Intramuscular Ziprasidone (2 mg and 20 mg) in Subjects with Psychosis and Acute Agitation Report Date: 21 November 1997.

5. IM CER Section 6.2 Studies 128-125, 128-126.

6. Study 128-120.

7. Study 128-121.

8. Study 128-306.

9. Addendum to IM CER Section 4.2 and 4.4.

10. IM CER Section 5.8.

11. Capsules CER Section 3.3.4 Study 128-030.

12. Capsules CER Section 3.3.6 and Appendix Z (Population Pharmacokinetics).

13. Capsules Cardiovascular MRP Assessment Report, Appendix III, page 13.

14. Capsules Cardiovascular MRP Assessment Report, Appendix III, pages 7-13.

15. FDA Psychopharmacological Drugs Advisory Committee, 19 July 2000, Briefing Document for Zeldox Capsules, page 68.

16. IM Cardiovascular MRP Assessment Report, Appendix I, page 11.

17. CPMP/986/96 Point to Consider: The Assessment of The Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products.

18. Statement deleted from section 4.4 (Special warnings and precautions for use) (28Feb05): In premarketing clinical trials there were no reported cases of NMS in patients receiving ziprasidone intramuscular injection. – Capsules CER Section 5.6.8.

19. Capsules CER Section 5.6.1.

20. Addendum to IM CER Section 3.6.

21. Addendum to IM CER Section 3.6.

22. Capsules CER Section 5.6.3.

23. Final Study Report: In Vitro Studies on the Metabolic Clearance Mechanisms of Ziprasidone and Major Circulating Metabolites in Human (Study DM2000-128-42), version August 10, 2000.

24. Study 128-048.

25. Study 128-203.

26. Study 128-025.

27. Study DM-94-128-5.

28. Study DM-94-128-31.

29. Study DM-96-128-36.

30. Paragraph deleted from section 4.5 (Interaction with other medicinal products and other forms of interaction) per ziprasidone team when IPI was retired (22 Sep 06): Ziprasidone is metabolized by aldehyde oxidase and to a lesser extent by CYP3A4. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase. – Study DM2000-128-42.

31. Study 128-050.

32. Study 128-049.

33. Study 128-039.

34. Paragraph deleted from section 4.5 (Interaction with other medicinal products and other forms of interaction) per ziprasidone team when IPI was retired (22Sep06): Benztropine, Propranolol and Lorazepam – Pharmacokinetic evaluation of ziprasidone serum concentrations of patients in clinical trials has not revealed any evidence of clinically significant interactions with benztropine, propranolol or lorazepam. – Capsule CER Section 3.3.6 and Appendix Z (Population Pharmacokinetics).

35. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): Reproductive toxicity studies with oral ziprasidone have not shown adverse effects on the reproductive process, other than those secondary to maternal toxicity resulting from an exaggerated pharmacological effect at doses equal to or greater than 17.5 times the maximum recommended human dose (MRHD) – Study 92-720-17.

36. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): Reproductive toxicity studies with oral ziprasidone have not shown adverse effects on the reproductive process, other than those secondary to maternal toxicity resulting from

an exaggerated pharmacological effect at doses equal to or greater than 17.5 times the maximum recommended human dose (MRHD) – Study 92-720-20.

37. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): There was no evidence of teratogenicity at any dose level (see Section 5.3 Preclinical Safety Data). – Study 91096/7.

38. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): There was no evidence of teratogenicity at any dose level (see Section 5.3 Preclinical Safety Data). – Study 94-720-30.

39. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): There was no evidence of teratogenicity at any dose level (see Section 5.3 Preclinical Safety Data). – Study 95-720-34.

40. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): There was no evidence of teratogenicity at any dose level (see Section 5.3 Preclinical Safety Data). – Study 91094/5.

41. Capsules CER Section 5.6.12.

42. Capsules CER Section 5.6.12.

43. IM CER Section 5.6.5.

44. Paragraph deleted from section 4.9 (Overdose) (28Feb05): In the largest overdose reported during pre-marketing clinical trials, a patient experienced sedation, slurred speech and transitory hypertension (200/95 mmHg) following ingestion of a confirmed 3240 mg of oral ziprasidone. The maximum observed QTc interval was 478 msec, six hours post-ingestion. No clinically significant changes in cardiac rhythm or function were observed and the patient was discharged following overnight observation in the emergency room. – American Journal of Psychiatry 157:5, May 2000, page 835.

45. Paragraph deleted from section 4.9 (Overdose) (28Feb05): In the largest overdose reported during pre-marketing clinical trials, a patient experienced sedation, slurred speech and transitory hypertension (200/95 mmHg) following ingestion of a confirmed 3240 mg of oral ziprasidone. The maximum observed QTc interval was 478 msec, six hours post-ingestion. No clinically significant changes in cardiac rhythm or function were observed and the patient was discharged following overnight observation in the emergency room. – AEM report #9907409, Study ZIP-NY-97-002.

46. Capsules CER Section 5.6.5.

47. Capsules Pharmacotoxicological Expert Report (PER) Section 2.1.

48. Capsules PER Section 2.1.

49. Capsules CER Section 3.2.1 Studies 128-202, 128-017.

50. IM CER Section 3.3 Studies 128-037, 128-038, 128-046.

51. Capsules CER Section 3.3.3.

52. CER Section 3.3.2 Studies DM-94-128-5, DM-128-31, DM-94-128-36.

53. Response to MPA Pharmacokinetic Assessor's Request 07Jul2000.

54. Capsules Pharmacokinetic MRP Assessment Report II, p. 32, Study DM2000-128-42.

55. Study 128-054.

56. Capsules CER Section 3.3.4 Study 128-028.

57. Capsules CER Section 3.3.6 and Appendix Z (Population Pharmacokinetics); PER Section 2.1.8 Studies DM95-128-29, DM95-128-33.

58. Study 128-026.

59. IM CER Section 5.8.

60. Study 128-030.

61. Capsules PER Section 4 Studies 92-720-17; 92-720-20; 91094/5; 91096/7; 94-720-30; 95-720-34; 89-720-07; 89-720-09; 92-720-18; 89-720-06; 89-720-10; 92-720-26; 88-720-01; 92114; 92-720-21.

62. Table MRP-2 request. Incidence of Categorical Bazett QTc Increases. Phase II/III Oral Ziprasidone Studies to 5 February 2001. Ziprasidone MRP-2.

63. Worldwide Labeling Safety Report, Hypotension Postural/Dizziness Postural and Ziprasidone dated 19Jun2002.

64. Worldwide Labeling Safety Report, Vomiting and Ziprasidone dated 19Jun2002.

65. Worldwide Labeling Safety Report, Tachycardia and Ziprasidone dated 19Jun2002.

66. Worldwide Labeling Safety Report, Insomnia and Ziprasidone dated 19Jun2002.

67. Worldwide Labeling Safety Report, Rash, Rash Maculopapular, Rash Erythematous and Ziprasidone dated 19Jun2002.

68. FINAL STUDY REPORT: PROTOCOL 128-037 Phase I Open Study to Compare The Pharmacokinetics of Ziprasidone Administered Intravenously, Intramuscularly and Orally to Healthy Subjects. Report Date: 15 January 1997.

69. FINAL STUDY REPORT: PROTOCOL 128-038 Phase I Investigator-Blind, Placebo-Controlled Evaluation of the Safety, Toleration and Pharmacokinetics of Ziprasidone Mesilate Following Single Cyclodextrin-Based (SBECD) Intramuscular Doses in Healthy Subjects. REPORT DATE: 2 December 1996.

70. FINAL STUDY REPORT: ZIPRASIDONE PROTOCOL A1281063 Single Blind, Parallel, Multicenter Study to Characterize the Pharmacokinetics and QTc Effects of Ziprasidone and

Haloperidol Following Intramuscular Administration to Subjects with Schizophrenia or Schizoaffective Disorder. REPORT DATE: 18 December 2001.

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