For the use only of Registered Medical Practitioner or a Hospital or a Laboratory Only

RESPIDON

1. Generic Name:

Risperidone Tablets I.P.

2. Qualitative and quantitative composition:

RESPIDON-1

Each film coated tablet contains:

Risperidone I.P……1mg

Colour: Titanium dioxide I.P.

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose., Talc, Colloidal Silicon Dioxide, Titanium dioxide

RESPIDON-2

Each film coated tablet contains:

Risperidone I.P……... 2mg

Colours: Lake of sunset yellow and Titanium dioxide I.P.

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose, Talc, Polyethylene Glycol, Lake of sunset yellow, Titanium Dioxide.

RESPIDON-3

Each film coated tablet contains:

Risperidone I.P……3mg

Colors: Lake of Tartrazine and Titanium dioxide I.P.

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose, Talc, Polyethylene Glycol, Lake of Tartrazine, Titanium Dioxide

RESPIDON-4

Each film coated tablet contains:

Risperidone I.P..……..4mg

Colors: Lake of Tartrazine, Lake of brilliant blue and Titanium dioxide I.P

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Wincoat WT-3066 Green, Methanol, Methylene Chloride.

3. Dosage form and strength:

Dosage form: Film coated tablet

Strength: 1, 2, 3, 4, mg

4. Clinical particulars:

4.1 Therapeutic indication:

- Schizophrenia
- RESPIDON is indicated for the acute and maintenance treatment of schizophrenia. Adolescents RESPIDON is indicated for the treatment of schizophrenia in adolescents aged 13–17 years.

4.2 Posology and method of administration:

Posology

Schizophrenia

Adults

Respidon may be given once daily or twice daily.

Patients should start with 2 mg/day RESPIDON. The dosage may be increased on the second day to 4 mg. Subsequently, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated, and are therefore not recommended.

Elderly

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

Paediatric population

RESPIDON is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of RESPIDON.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

Respidon should be used with caution in these groups of patients.

Method of administration

- Respidon is for oral use. Food does not affect the absorption of Respidon.
- Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported.
- Switching from other antipsychotics.
- When medically appropriate, gradual discontinuation of the previous treatment while Respidon therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Respidon therapy in place of the

next scheduled injection. The need for continuing existing anti-Parkinson medicines should be reevaluated periodically.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use:

- Elderly patients with dementia
- Increased mortality in elderly people with dementia
- In a meta-analysis of 17 controlled trials of atypical antipsychotics, including RESPIDON, elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral RESPIDON in this population, the incidence of mortality was 4.0% for RESPIDON - treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100). Data from two large observational studies showed that elderly people with dementia who are treated with conventional antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
- Concomitant use with furosemide
- In the RESPIDON placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus RESPIDON (7.3%; mean age 89 years, range 75-97) when compared to patients treated with RESPIDON alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus RESPIDON was observed in two of the four clinical trials. Concomitant use of RESPIDON with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.
- No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with RESPIDON. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia. Cerebrovascular Adverse Events (CVAE)
- An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with RESPIDON in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with RESPIDON and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. RESPIDON should be used with caution in patients with risk factors for stroke.

- The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with RESPIDON.
- Physicians are advised to assess the risks and benefits of the use of RESPIDON in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of RESPIDON.
- RESPIDON should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.
- Patients should be reassessed regularly, and the need for continuing treatment reassessed.
- Orthostatic hypotension
- Due to the alpha-blocking activity of Respidon, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of Respidon and antihypertensive treatment. Respidon should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.
- Leukopenia, neutropenia, and agranulocytosis
- Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including Respidon. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance.
- Patients with a history of a clinically significant low white blood cell count (WBC) or a druginduced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of Respidon should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
- Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 109/L) should discontinue Respidon and have their WBC followed until recovery.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

- Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Neuroleptic malignant syndrome (NMS)

- Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include

myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including Respidon, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

- Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RESPIDON, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with Respidon. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycaemia and diabetes mellitus

- Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with Respidon. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including RESPIDON, should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.
- Weight gain
- Significant weight gain has been reported with Respidon use. Weight should be monitored regularly.

Hyperprolactinaemia

- Hyperprolactinaemia is a common side-effect of treatment with Respidon. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side-effects (e.g. gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhea).
- Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Respidon should be used with caution in patients with preexisting hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

- QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when Respidon is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.
- Seizures
- Respidon should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

- Priapism
- Priapism may occur with RESPIDON treatment due to its alpha-adrenergic blocking effects.
- Body temperature regulation
- Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing RESPIDON to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

- An antiemetic effect was observed in preclinical studies with RESPIDON. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Renal and hepatic impairment

- Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of RESPIDON.

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 RESPIDON and preventative measures undertaken.

Intraoperative Floppy Iris Syndrome

- Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including RESPIDON.
- IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Paediatric population

- Before RESPIDON is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.
- The sedative effect of RESPIDON should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of RESPIDON could improve the impact of the sedation on attention faculties of children and adolescents. RESPIDON was associated with mean increases in body weight and body mass index (BMI). Baseline weight measurement prior to treatment and regular weight monitoring are recommended. Changes in height in the long-term open-label extension studies were within expected age-appropriate norms.

The effect of long-term RESPIDON treatment on sexual maturation and height has not been adequately studied.

- Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.
- Results from a small post-marketing observational study showed that RESPIDON-exposed subjects between the ages of 8-16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical anti-psychotic medications. This study was not adequate to determine whether exposure to RESPIDON had any impact on final adult height, or whether the result was due to a direct effect of RESPIDON on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying disease with resulting increase in linear growth.
- During treatment with RESPIDON regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.
- For specific posology recommendations in children and adolescents.

4.5 Drug-Interaction:

Pharmacodynamic-related Interactions

- Drugs known to prolong the QT interval
- As with other antipsychotics, caution is advised when prescribing RESPIDON with medicinal products known to prolong the QT interval, such as antiarrhythmics (e.g., quinidine, dysopiramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of RESPIDON. This list is indicative and not exhaustive.

Centrally-Acting Drugs and Alcohol

- RESPIDON should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and Dopamine Agonists

- RESPIDON may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Drugs with Hypotensive Effect

Clinically significant hypotension has been observed postmarketing with concomitant use of RESPIDON and antihypertensive treatment.

Psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with reisperidone can lead to extrapyramidal symptoms upon change of either or both tratments.

Paliperidone

Concomitant use of oral RESPIDON with paliperidone is not recommended as paliperidone is the active metabolite of RESPIDON and the combination of the two may lead to additive active antipsychotic fraction exposure.

Pharmacokinetic-related Interactions

Food does not affect the absorption of RESPIDON.
RESPIDON is mainly metabolized through CYP2D6, and to a lesser extent through CYP3A4. Both RESPIDON and its active metabolite 9-hydroxyRESPIDON are substrates of Pglycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the RESPIDON active antipsychotic fraction.

Strong CYP2D6 Inhibitors
Co-administration of RESPIDON with a strong CYP2D6 inhibitor may increase the plasma concentrations of RESPIDON, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the RESPIDON active antipsychotic fraction (e.g., paroxetine, see below). It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of RESPIDON in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of RESPIDON.

CYP3A4 and/or P-gp Inhibitors
Co-administration of RESPIDON with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the RESPIDON active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of RESPIDON.
CYP3A4 and/or P-gp Inducers
Co-administration of RESPIDON with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the RESPIDON active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of RESPIDON. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.
Highly Protein-bound Drugs
When RESPIDON is taken together with highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosage.
Paediatric Population
Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.
The combined use of psychostimulants (e.g., methylphenidate) with RESPIDON in children and adolescents did not alter the pharmacokinetics and efficacy of RESPIDON.
Examples of drugs that may potentially interact or that were shown not to interact with RESPIDON are listed below:
Effect of other medicinal products on the pharmacokinetics of RESPIDON Antibacterials:

- Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of RESPIDON and the active antipsychotic fraction.
- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.
- Anticholinesterases:

- Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of RESPIDON and the active antipsychotic fraction.
- Antiepileptics:
- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of RESPIDON. Similar effects may be observed with e.g. phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme, as well as P-glycoprotein.
- Topiramate modestly reduced the bioavailability of RESPIDON, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.
- Antifungals:
- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at RESPIDON doses of 2 to 8 mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of RESPIDON and decreased the plasma concentrations of 9-hydroxyRESPIDON. Antipsychotics:
- Phenothiazines may increase the plasma concentrations of RESPIDON but not those of the active antipsychotic fraction.
- Antivirals:
- Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the RESPIDON active antipsychotic fraction.
- Beta blockers:
- Some beta-blockers may increase the plasma concentrations of RESPIDON but not those of the active antipsychotic fraction.
- Calcium channel blockers:
- Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of RESPIDON and the active antipsychotic fraction.
- Gastrointestinal drugs:
- H2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of RESPIDON, but only marginally that of the active antipsychotic fraction.
- SSRIs and Tricyclic antidepressants:
- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of RESPIDON, but less so of the active antipsychotic fraction.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of RESPIDON, but, at dosages up to 20 mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the RESPIDON active antipsychotic fraction. • Tricyclic antidepressants may increase the plasma concentrations of RESPIDON but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of RESPIDON or the active antipsychotic fraction.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the RESPIDON active antipsychotic fraction. However, doses higher

than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the RESPIDON active antipsychotic fraction.

- Effect of RESPIDON on the pharmacokinetics of other medicinal products Antiepileptics:
- RESPIDON does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate. Antipsychotics:
- Aripiprazole, a CYP2D6 and CYP3A4 substrate: RESPIDON tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.
- Digitalis glycosides:
- RESPIDON does not show a clinically relevant effect on the pharmacokinetics of digoxin. Lithium:
- RESPIDON does not show a clinically relevant effect on the pharmacokinetics of lithium.
- Concomitant use of RESPIDON with furosemide
- regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6 Use in special populations (Fertility, Pregnancy And Lactation)

Pregnancy

There are no adequate data from the use of RESPIDON in pregnant women. RESPIDON was not teratogenic in animal studies but other types of reproductive toxicity were seen. The potential risk for humans is unknown.

Neonates exposed to antipsychotics (including RESPIDON) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

RESPIDON should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breast-feeding

In animal studies, RESPIDON and 9-hydroxy-RESPIDON are excreted in the milk. It has been demonstrated that RESPIDON and 9-hydroxy-RESPIDON are also excreted in human breast milk in small quantities. There are no data available on adverse reactions in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

Fertility

As with other drugs that antagonize dopamine D2 receptors, RESPIDON elevates prolactin level. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

There were no relevant effects observed in the non-clinical studies**.**

4.7 Effects on ability to drive and use machines:

RESPIDON can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known**.**

4.8 Undesirable effects:

The most frequently reported adverse drug reactions (ADRs) (incidence ≥10%) are:

Parkinsonism, sedation/somnolence, headache and insomnia.

The ADRs that appeared to be dose-related included parkinsonism and akathisia.

The following are all the ADRs that were reported in clinical trials and postmarketing experience with RESPIDON by frequency category estimated from RESPIDON clinical trials. The following terms and frequencies are applied: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Adverse Drug Reaction**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Infections and infestations		pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear	respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis,	infection	
Blood and lymphatic system disorders			neutropenia, white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased, eosinophil count increased	agranulocytosis[c]	
Immune system disorders			hypersensitivity	anaphylactic reaction[c]	

Endocrine disorders		hyperprolactinaemia [a]		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition disorders		weight increased, increased appetite, decreased appetite	diabetes mellitus [b], hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased	water intoxication[c], hypoglycemia, hyperinsulinaemia[c], blood triglycerides increased	diabetic ketoacidosis
Psychiatric disorders	insomnia[d]	sleep disorder, agitation, depression, anxiety	mania, confusional state, libido decreased, nervousness, nightmare	blunted affect, anorgasmia	
Nervous system disorders	sedation/ somnolence, parkinsonism [d], headache	akathisia[d], dystonia[d], dizziness, dyskinesia[d], tremor	tardive dyskinesia, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness,	neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation	

			convulsion[d], syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia		
Eye disorders		vision blurred, conjunctivitis	photophobia, dry eye, lacrimation increased, ocular hyperaemia	glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)[c]	
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac disorders		Tachycardia	atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, palpitations	sinus arrhythmia	

Vascular disorders		Hypertension	hypotension, orthostatic hypotension, flushing	pulmonary embolism, venous thrombosis	
Respiratory, thoracic and mediastinal disorders		dyspnoea, pharyngolaryngeal pain, cough,	pneumonia aspiration, pulmonary congestion,	sleep apnoea syndrome, hyperventilation	
		epistaxis, nasal congestion	respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder		
Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence	pancreatitis, intestinal obstruction, swollen tongue, cheilitis	ileus
Skin and subcutaneous tissue disorders		rash, erythema	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin lesion	drug eruption, dandruff	angioedema

Musculoskeletal and connective tissue disorders		muscle spasms, musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain	rhabdomyolysis	
Renal and urinary disorders		urinary incontinence	pollakiuria, urinary retention, dysuria		
Pregnancy, puerperium, and neonatal conditions				drug withdrawal syndrome neonatal[c]	
Reproductive system and breast disorders			erectile dysfunction, ejaculation disorder,	priapism[c], menstruation delayed, breast engorgement,	
			amenorrhoea, menstrual disorder[d], gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge	breast enlargement, breast discharge	

General disorders and administration site conditions		oedema[d], pyrexia, chest pain, asthenia, fatigue, pain	face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort	hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration[c]	
Hepatobiliary disorders			transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased	jaundice	
Injury, poisoning and procedural complications		Fall	procedural pain		

Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances amenorrhoea, anovulation, galactorrhea, fertility disorder, decreased libido, erectile dysfunction.

In placebo-controlled trials diabetes mellitus was reported in 0.18% in RESPIDON-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all RESPIDON-treated subjects.

Not observed in RESPIDON clinical studies but observed in post-marketing environment with RESPIDON.

Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia.

Dystonia includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin. **Insomnia** includes: initial insomnia, middle insomnia; **Convulsion** includes: Grand mal

convulsion; **Menstrual disorder** includes:Menstruation irregular, oligomenorrhoea; **Oedema** includes: generalised oedema, oedema peripheral, pitting oedema.

Undesirable effects noted with paliperidone formulations

Paliperidone is the active metabolite of RESPIDON, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, the following adverse reaction has been noted with the use of paliperidone products and can be expected to occur with RESPIDON. **Cardiac disorders:** Postural orthostatic tachycardia syndrome

Class effects

As with other antipsychotics, very rare cases of QT prolongation have been reported postmarketing with RESPIDON. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

Venous thromboembolism

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs (frequency unknown).

Weight gain

The proportions of RESPIDON and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RESPIDON (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the RESPIDON (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

In a population of children and adolescents with conduct and other disruptive behaviour disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5 kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.

Additional information on special populations

Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:

Elderly patients with dementia

Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

Paediatric population

In general, type of adverse reactions in children is expected to be similar to those observed in adults.

The following ADRs were reported with a frequency ≥5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal

pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis. The effect of long-term RESPIDON treatment on sexual maturation and height has not been adequately studied.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose:

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of RESPIDON. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of RESPIDON and paroxetine.

In case of acute overdose, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to RESPIDON. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. Pharmacological properties:

5.1 Mechanism of Action:

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08

Mechanism of action

RESPIDON is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2and dopaminergic D2 receptors. RESPIDON binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2adrenergic receptors. RESPIDON has no affinity for cholinergic receptors. Although RESPIDON is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacodynamic properties:

Clinical efficacy

Schizophrenia

The efficacy of RESPIDON in the short-term treatment of schizophrenia was established in four studies, 4- to 8-weeks in duration, which enrolled over 2500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of RESPIDON in doses up to

10 mg/day administered twice daily, RESPIDON was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8-week, placebo-controlled trial involving four fixed doses of RESPIDON (2, 6, 10, and 16 mg/day, administered twice daily), all four RESPIDON groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial involving five fixed doses of RESPIDON (1, 4, 8, 12, and 16 mg/day administered twice-daily), the 4, 8, and 16 mg/day RESPIDON dose groups were superior to the 1 mg RESPIDON dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of RESPIDON (4 and 8 mg/day administered once daily), both RESPIDON dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (>20% reduction in PANSS total score). In a longer-term trial, adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to RESPIDON 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving RESPIDON experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.

Manic episodes in bipolar disorder

The efficacy of RESPIDON monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSMIV criteria. In the three studies, RESPIDON 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in total Young Mania Rating Scale (YMRS) score at Week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of ≥ 50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for RESPIDON than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between RESPIDON and haloperidol at Week 12.

The efficacy of RESPIDON in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, RESPIDON 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at Week 3. In a second 3-week study, RESPIDON 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of RESPIDON and 9-hydroxy-RESPIDON clearance by carbamazepine, leading to subtherapeutic levels of RESPIDON and 9-hydroxy-RESPIDON. When the carbamazepine group was excluded in a post-hoc analysis, RESPIDON combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Persistent aggression in dementia

The efficacy of RESPIDON in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1150 elderly patients with moderate to severe dementia. One study included fixed RESPIDON doses of 0.5, 1, and 2 mg/day. Two flexible-dose studies included RESPIDON dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/day, respectively. RESPIDON showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's

Disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of RESPIDON was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of RESPIDON; of the presence or absence of psychosis; and of the type of dementia, Alzheimer's, vascular, or mixed.

Paediatric population
Conduct disorder
The efficacy of RESPIDON in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5 to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or mild or moderate mental retardation/learning disorder. In the two studies, RESPIDON 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at Week 6.

5.3 Pharmacokinetic properties:

RESPIDON orodispersible tablets and oral solution are bio-equivalent to RESPIDON filmcoated tablets.
RESPIDON is metabolised to 9-hydroxy-RESPIDON, which has a similar pharmacological activity to RESPIDON (see Biotransformation and Elimination).

Absorption
RESPIDON is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of RESPIDON is 70% (CV=25%). The relative oral bioavailability of RESPIDON from a tablet is 94% (CV=10%) compared with a solution. The absorption is not affected by food and thus RESPIDON can be given with or without meals. Steady-state of RESPIDON is reached within 1 day in most patients. Steady-state of 9-hydroxy-RESPIDON is reached within 4-5 days of dosing.

Distribution
RESPIDON is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, RESPIDON is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of RESPIDON is 90%, that of 9-hydroxy-RESPIDON is 77%.

Biotransformation and elimination
RESPIDON is metabolised by CYP 2D6 to 9-hydroxy-RESPIDON, which has a similar pharmacological activity as RESPIDON. RESPIDON plus 9-hydroxy-RESPIDON form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert RESPIDON rapidly into 9-hydroxy-RESPIDON, whereas poor CYP 2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower RESPIDON and higher 9-hydroxy-RESPIDON concentrations than poor metabolisers, the pharmacokinetics of RESPIDON and 9-hydroxy-RESPIDON combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.
Another metabolic pathway of RESPIDON is N-dealkylation. In vitro studies in human liver microsomes showed that RESPIDON at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, RESPIDON plus 9-hydroxy-RESPIDON represent 35-45% of the dose. The remainder is inactive metabolites. After oral

administration to psychotic patients, RESPIDON is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-RESPIDON and of the active antipsychotic fraction is 24 hours.

Linearity/non-linearity

RESPIDON plasma concentrations are dose-proportional within the therapeutic dose-range.

Elderly, hepatic and renal impairment

A single-dose PK-study with oral RESPIDON showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly.

In adults with moderate renal disease the clearance of the active moiety was ~48% of the clearance in young healthy adults. In adults with severe renal disease the clearance of the active moiety was ~31% of the clearance in young healthy adults. The half-life of the active moiety was 16.7 h in young adults, 24.9 h in adults with moderate renal disease (or ~1.5 times as long as in young adults), and 28.8 h in those with severe renal disease (or ~1.7 times as long as in young adults). RESPIDON plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of RESPIDON in plasma was increased by 37.1%. The oral clearance and the elimination half-life of RESPIDON and of the active moiety in adults with moderate and severe liver impairment were not significantly different from those parameters in young healthy adults.

Paediatric population

The pharmacokinetics of RESPIDON, 9-hydroxy-RESPIDON and the active antipsychotic fraction in children are similar to those in adults.

Gender, race and smoking habits

A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of RESPIDON or the active antipsychotic fraction.

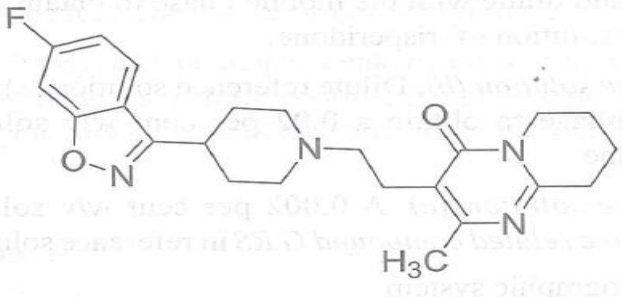
6. Nonclinical properties:

In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D2-receptor blocking activity of RESPIDON. In addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. RESPIDON was not teratogenic in rat and rabbit. In rat reproduction studies with RESPIDON, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to RESPIDON was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring. In a toxicity study in juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Based on AUC, long bone growth was not affected in dogs at 3.6-times the maximum human exposure in adolescents (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human exposure in adolescents.

RESPIDON was not genotoxic in a battery of tests. In oral carcinogenicity studies of RESPIDON in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown. In vitro and in vivo, animal models show that at high doses RESPIDON may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

7. Description:

Risperidone is 3-[2—[4-(6-Fluoro-1,2-benzisoxazol-3-y)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.Having molecular weight 410.5 and molecular formula $C_{23}H_{27}FN_4O_2$. The molecular structure is:



Risperidone is a white or almost white powder. It is soluble in methylene chloride; sparingly soluble in alcohol; practically insoluble in water.

Product Description:

RESPIDON 1: White coloured, round, biconvex, film-coated tablets with bisecting line on one side. The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose., Talc, Colloidal Silicon Dioxide, Titanium dioxide.

RESPIDON 2: Light orange coloured, round, biconvex, film-coated tablets with bisecting line on one side. The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose, Talc, Polyethylene Glycol, Lake of sunset yellow, Titanium Dioxide.

RESPIDON 3: Light yellow coloured, round, biconvex, film-coated tablets with bisecting line on one side. The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose, Talc, Polyethylene Glycol, Lake of Tartrazine, Titanium Dioxide.

RESPIDON 4: Light green coloured, round, biconvex, film-coated tablets with bisecting line on one side. The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Wincoat WT-3066 Green, Methanol, Methylene Chloride.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

Not applicable.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

RESPIDON are available as blister strip of 10 tablets.

8.4 Storage and handing instructions:

Store at a temperature not exceeding 30°C, protected from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

RESPIDON

Risperidone Tablets IP

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What RESPIDON is and what it is used for

RESPIDON belongs to a group of medicines called 'antipsychotics'.
RESPIDON is used to treat the following:

- Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder"
- Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer's dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously
- Short-term treatment (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder.
- RESPIDON can help alleviate the symptoms of your disease and stop your symptoms from coming back.

9.2 What RESPIDON is and what it is used for

Do not take RESPIDON

- If you are allergic (hypersensitive) to risperidone or any of the other ingredients of this medicine (listed in section 9.6).

If you are not sure if the above applies to you, talk to your doctor or pharmacist before using RESPIDON.

Warnings and precautions

Talk to your doctor or pharmacist before taking RESPIDON if:

- You have a heart problem. Examples include an irregular heart rhythm or if you are prone to low blood pressure or if you are using medicines for your blood pressure. RESPIDON may cause low blood pressure. Your dose may need to be adjusted
- You know of any factors which would favour you having a stroke, such as high blood pressure, cardiovascular disorder or blood vessel problems in the brain
- You have ever experienced involuntary movements of the tongue, mouth and face
- You have ever had a condition whose symptoms include high temperature, muscle stiffness, sweating or a lowered level of consciousness (also known as Neuroleptic Malignant Syndrome)
- You have Parkinson's disease or dementia
- You know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines)
- You are diabetic
- You have epilepsy
- You are a man and you have ever had a prolonged or painful erection
- You have problems controlling your body temperature or overheating
- You have kidney problems
- You have liver problems
- You have an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour.
- You or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using RESPIDON.

As dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood has been seen very rarely with patients taking RESPIDON, your doctor may check your white blood cell counts.

RESPIDON may cause you to gain weight. Significant weight gain may adversely affect your health. Your doctor should regularly measure your body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking RESPIDON, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

RESPIDON commonly raises levels of a hormone called "prolactin". This may cause side effects such as menstrual disorders or fertility problems in women, breast swelling in men (see Possible side effects). If such side effects occur, evaluation of the prolactin level in the blood is recommended.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

Elderly people with dementia

In elderly patients with dementia, there is an increased risk of stroke. You should not take risperidone if you have dementia caused by stroke.

During treatment with risperidone you should frequently see your doctor.

Medical treatment should be sought straight away if you or your caregiver notice a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.

Children and adolescents

Before treatment is started for conduct disorder, other causes of aggressive behaviour should have been ruled out.

If during treatment with risperidone tiredness occurs, a change in the time of administration might improve attention difficulties.
Before treatment is started your, or your child's body weight may be measured and it may be regularly monitored during treatment.
A small and inconclusive study has reported an increase in height in children who took risperidone, but whether this is an effect of the drug or due to some other reason is not known.

Other medicines and RESPIDON

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is especially important to talk to your doctor or pharmacist if you are taking any of the following

- Medicines that work on your brain such as to help you calm down (benzodiazepines) or some medicines for pain (opiates), medicines for allergy (some antihistamines), as risperidone may increase the sedative effect of all of these
- Medicines that may change the electrical activity of your heart, such as medicines for malaria, heart rhythm problems, allergies (antihistamines), some antidepressants or other medicines for mental problems
- Medicines that cause a slow heart beat
- Medicines that cause low blood potassium (such as certain diuretics)
- Medicines to treat raised blood pressure. RESPIDON can lower blood pressure
- Medicines for Parkinson's disease (such as levodopa)
- Medicines that increase the activity of the central nervous system (psychostimulants, such as methylphenidate)
- Water tablets (diuretics) used for heart problems or swelling of parts of your body due to a build up of too much fluid (such as furosemide or chlorothiazide). RESPIDON taken by itself or with furosemide, may have an increased risk of stroke or death in elderly people with dementia.

The following medicines may reduce the effect of risperidone

- Rifampicin (a medicine for treating some infections)
- Carbamazepine, phenytoin (medicines for epilepsy)
- Phenobarbital.

If you start or stop taking such medicines you may need a different dose of risperidone.

The following medicines may increase the effect of risperidone

- Quinidine (used for certain types of heart disease)
- Antidepressants such as paroxetine, fluoxetine, tricyclic antidepressants
- Medicines known as beta-blockers (used to treat high blood pressure)
- Phenothiazines (such as medicines used to treat psychosis or to calm down)
- Cimetidine, ranitidine (blockers of the acidity of stomach)
- Itraconazole and ketoconazole (medicines for treating fungal infections)
- Certain medicines used in the treatment of HIV/AIDS, such as ritonavir
- Verapamil, a medicine used to treat high blood pressure and/or abnormal heart rhythm
- Sertraline and fluvoxamine, medicines used to treat depression and other psychiatric disorders. If you start or stop taking such medicines you may need a different dose of risperidone.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using RESPIDON.

RESPIDON with food, drink and alcohol

You can take this medicine with or without food. You should avoid drinking alcohol when taking RESPIDON.

Pregnancy, breast-feeding and fertility

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will decide if you can take it
- The following symptoms may occur in newborn babies, of mothers that have used RESPIDON in the last trimester (last three months of their pregnancy): shaking, muscle stiffness, and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
- RESPIDON can raise your levels of a hormone called "prolactin" that may impact fertility (see Possible side effects).

Driving and using machines

Dizziness, tiredness, and vision problems may occur during treatment with RESPIDON. Do not drive or use any tools or machines without talking to your doctor first.

9.3 What RESPIDON is and what it is used for

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is as follows:

For the treatment of schizophrenia

Adults

- The usual starting dose is 2 mg per day, this may be increased to 4 mg per day on the second day
- Your dose may then be adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with daily doses of 4 to 6 mg
- This total daily dose can be divided into either one or two doses a day. Your doctor will tell you which is the best for you.

Elderly people

- Your starting dose will normally be 0.5 mg twice a day
- Your dose may then be gradually increased by your doctor to 1 mg to 2 mg twice a day
- Your doctor will tell you which is the best for you.

For the treatment of mania

Adults

- Your starting dose will usually be 2 mg once a day
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with doses of 1 to 6 mg once a day.

Elderly people

- Your starting dose will usually be 0.5 mg twice a day
- Your dose may then be gradually adjusted by your doctor to 1 mg to 2 mg twice a day depending on how much you respond to the treatment.

For the treatment of long-standing aggression in people with Alzheimer's dementia

Adults (including elderly people)

- Your starting dose will normally be 0.25 mg (0.25 ml of RESPIDON oral solution 1 mg/ml) twice a day
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with 0.5 mg twice a day. Some patients may need 1 mg twice a day
- Treatment duration in patients with Alzheimer's dementia should be not more than 6 weeks.

Use in children and adolescents

- Children and adolescents under 18 years old should not be treated with RESPIDON for schizophrenia or mania.

For the treatment of conduct disorder

The dose will depend on your child's weight:

For children who weigh less than 50 kg

- The starting dose will normally be 0.25 mg (0.25 ml of RESPIDON oral solution 1 mg/ml) once a day
- The dose may be increased every other day in steps of 0.25 mg per day.
- The usual maintenance dose is 0.25 mg to 0.75 mg (0.25 ml to 0.75 ml of RESPIDON oral solution 1 mg/ml) once a day.

For children who weigh 50 kg or more

- The starting dose will normally be 0.5 mg once a day
- The dose may be increased every other day in steps of 0.5 mg per day.
- The usual maintenance dose is 0.5 mg to 1.5 mg once a day.

Treatment duration in patients with conduct disorder should be not more than 6 weeks.
Children under 5 years old should not be treated with RESPIDON for conduct disorder.

People with kidney or liver problems

Regardless of the disease to be treated, all starting doses and following doses of risperidone should be halved. Dose increases should be slower in these patients.
Risperidone should be used with caution in this patient group.

Method of administration

For oral use

- You should swallow your tablet with a drink of water
- The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

If you take more RESPIDON than you should

- See a doctor right away. Take the medicine pack with you
- In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heartbeats or fits.

If you forget to take RESPIDON

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor

Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you stop taking RESPIDON

You should not stop taking this medicine unless told to do so by your doctor. Your symptoms may return. If your doctor decides to stop this medicine, your dose may be decreased gradually over a few days.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience any of the following uncommon side effects (may affect up to 1 in 100 people):

- Have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke

- Experience tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of RESPIDON may be needed **Tell your doctor immediately if you experience any of the following rare side effects (may affect up to 1 in 1,000 people):**
- Experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately
- Experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called
- "Neuroleptic Malignant Syndrome". Immediate medical treatment may be needed
- Are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed
- Experience severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash or drop in blood pressure.

The following other side effects may also happen:

Very common side effects (may affect more than 1 in 10 people):

- Difficulty falling or staying asleep
- Parkinsonism: This condition may include: slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face
- Feeling sleepy, or less alert
- Headache.

Common side effects (may affect up to 1 in 10 people):

- Pneumonia, infection of the chest (bronchitis), common cold symptoms, sinus infection, urinary tract infection, ear infection, feeling like you have the flu
- Raised levels of a hormone called "prolactin" found in a blood test (which may or may not cause symptoms). Symptoms of high prolactin occur uncommonly and may include in men breast swelling, difficulty in getting or maintaining erections, decreased sexual desire or other sexual dysfunction. In women they may include breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle or fertility problems
- Weight gain, increased appetite, decreased appetite
- Sleep disorder, irritability, depression, anxiety, restlessness
- Dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw
- Dizziness
- Dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching
- Tremor (shaking)
- Blurry vision, eye infection or "pink eye"
- Rapid heart rate, high blood pressure, shortness of breath
- Sore throat, cough, nose bleeds, stuffy nose
- Abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhea, indigestion, dry mouth, toothache
- Rash, skin redness
- Muscle spasms, bone or muscle ache, back pain, joint pain

- Incontinence (lack of control) of urine
- Swelling of the body, arms or legs, fever, chest pain, weakness, fatigue (tiredness), pain
- Fall.

Uncommon side effects (may affect up to 1 in 100 people):

- Infection of the breathing passages, bladder infection, ‘eye infection, tonsillitis, fungal infection of the nails, infection of the skin, an infection confined to a single area of skin or part of the body, viral infection, skin inflammation caused by mites
- Decrease in the type of white blood cells that help to protect you against infection, white blood cell count decreased, decrease in platelets (blood cells that help you stop bleeding), anemia, decrease in red blood cells, increase in eosinophils (a type of white blood cell) in your blood
- Allergic reaction
- Diabetes or worsening of diabetes, high blood sugar, excessive drinking of water
- Weight loss, loss of appetite resulting in malnutrition and low body weight
- Increased cholesterol in your blood
- Elated mood (mania), confusion, decreased sexual drive, nervousness, nightmares
- Unresponsive to stimuli, loss of consciousness, low level of consciousness
- Convulsion (fits), fainting
- A restless urge to move parts of your body, balance disorder, abnormal coordination, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness skin
- Oversensitivity of the eyes to light, dry eye, increased tears, redness of the eyes
- Sensation of spinning (vertigo), ringing in the ears, ear pain
- Atrial fibrillation (an abnormal heart rhythm), an interruption in conduction between the upper and lower parts of the heart, Abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, slow heart rate, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations)
- Low blood pressure, low blood pressure upon standing (consequently, some people taking taking
- RESPIDON may feel faint, dizzy, or may pass out when they stand up or sit up suddenly, flushing
- Pneumonia caused by inhaling food, lung congestion, congestion of breathing passages, crackly lung sounds, wheezing, voice disorder, breathing passage disorder
- Stomach or intestinal infection, stool incontinence, very hard stool, difficulty swallowing, Excessive passing of gas or wind
- Hives (or "nettle rash"), itching, hair loss, thickening of skin, eczema, dry skin, skin discoloration, acne, flaky, itchy scalp or skin, skin disorder, skin lesion
- An increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown
- Abnormal posture, joint stiffness, joint swelling, muscle weakness, neck pain
- Frequent passing of urine, inability to pass urine, pain when passing urine
- Erectile dysfunction, ejaculation disorder
- Loss of menstrual periods, missed menstrual periods or other problems with your cycle (females)
- Development of breasts in men, leakage of milk from the breasts, sexual dysfunction, breast pain, Breast discomfort, Vaginal discharge
- Swelling of the face, mouth, eyes, or lips
- Chills, an increase in body temperature
- A change in the way you walk
- Feeling thirsty, feeling unwell, chest discomfort, feeling "out of sorts", discomfort

- Increased liver transaminases in your blood, increased GGT (a liver enzyme called gammaglutamyltransferase) in your blood, increased liver enzymes in your blood
- Procedural pain.

Rare side effects (may affect up to 1 in 1,000 people):

- Infection
- Inappropriate secretion of a hormone that controls urine volume
- Sleep walking
- Sleep-related eating disorder
- Sugar in the urine, low blood sugar, high blood triglycerides (a fat)
- Lack of emotion, inability to reach orgasm
- Not moving or responding while awake (catatonia)
- Blood vessel problems in the brain
- Coma due to uncontrolled diabetes
- Shaking of the head
- Glaucoma (increased pressure within the eyeball), problems with movement of your eyes, eye rolling, eyelid margin crusting
- Eye problems during cataract surgery. During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you take or have taken RESPIDON. If you need to have cataract surgery, be sure to tell your eye doctor if you take or have taken this medicine
- Dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood
- Dangerously excessive intake of water
- Irregular heart beat
- Trouble breathing during sleep (sleep apnea), fast, shallow breathing
- Inflammation of the pancreas, a blockage in the bowels
- Swollen tongue, chapped lips, rash on skin related to drug
- Dandruff
- Breakdown of muscle fibers and pain in muscles (rhabdomyolysis)
- A delay in menstrual periods, enlargement of the glands in your breasts, breast enlargement, discharge from the breasts
- Increased insulin (a hormone that controls blood sugar levels) in your blood
- Hardening of the skin
- Decreased body temperature, coldness in arms and legs
- Symptoms of drug withdrawal
- Yellowing of the skin and the eyes (jaundice).

Very rare side effects (may affect up to 1 in 10,000 people):

- Life threatening complications of uncontrolled diabetes
- Serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing
- Lack of bowel muscle movement that causes blockage.
- The following side effect has been seen with the use of another medicine called paliperidone that is very similar to risperidone, so these can also be expected with RESPIDON: Rapid heartbeat upon standing.

Additional side effects in children and adolescents

In general, side effects in children are expected to be similar to those in adults.

The following side effects were reported more often in children and adolescents (5 to 17 years) than in adults: feeling sleepy, or less alert, fatigue (tiredness), headache, increased appetite, vomiting, common cold symptoms, nasal congestion, abdominal pain, dizziness, cough, fever, tremor (shaking), diarrhoea, and incontinence (lack of control) of urine.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store RESPIDON

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister, carton, or bottle. The expiry date refers to the last day of that month.
- Store at a temperature not exceeding 30°C, protected from light and moisture.
- Blister packs: Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information

What RESPIDON contains

The active substance is risperidone.
Each film-coated tablet contains either 1 mg, 2 mg, 3 mg, 4 mg of risperidone.
RESPIDON are available as blister strip of 10 tablets.

RESPIDON-1

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose., Talc, Colloidal Silicon Dioxide, Titanium dioxide.

RESPIDON-2

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose, Talc, Polyethylene Glycol, Lake of sunset yellow, Titanium Dioxide.

RESPIDON-3

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Hydroxy Propyl Methyl Cellulose, Talc, Polyethylene Glycol, Lake of Tartrazine, Titanium Dioxide.

RESPIDON-4

The excipients used are Lactose Monohydrate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Methanol, Starch, Wincoat WT-3066 Green, Methanol, Methylene Chloride.

10. Details of manufacturer

Torrent Pharmaceutical Ltd,

32 No Middle Camp, NH-10, East District, Gangtok, Sikkim-737 135.

Or

RESPIDON-1, 2, 3

Swiss Garnier Genexiaaa Sciences Pvt. Ltd.,

Plot No. 54 & 78 Mamring Bashti, Rangpo Post, South Sikkim-737132.

RESPIDON-4

Windlas Healthcare (P) Limited.

Plot No. 183 & 192, Mohabewala Industrial Area, Dehradun-248110, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic. No M/563/2010 issued on 04.Dec.2019

or

RESPIDON-1, 2, 3

Mfg Lic. No. M/605/2021 issued on 29.12.2017

RESPIDON-4

Mfg Lic. No. 47/UA/2009 issued on 25.09.2020

12. Date of revision

MAY 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/RESPIDONE 1, 2, 3, 4 mg/MAY-21/03/PI