

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Nodiril 0.5 mg film-coated tablets

Nodiril 1 mg film-coated tablets

Nodiril 2 mg film-coated tablets

Nodiril 3 mg film-coated tablets

Nodiril 4 mg film-coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nodiril 0.5 mg: Each film-coated tablet contains 0.5 mg risperidone

Nodiril 1 mg: Each film-coated tablet contains 1 mg risperidone.

Nodiril 2 mg: Each film-coated tablet contains 2 mg risperidone.

Nodiril 3 mg: Each film-coated tablet contains 3 mg risperidone.

Nodiril 4 mg: Each film-coated tablet contains 4 mg risperidone.

For excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film-coated tablet.

0.5 mg tablet: white, film-coated, round, biconvex tablet, diameter 6 mm.

1 mg tablet: white, film-coated, oval, biconvex, scored tablet, size 8 mm x 5 mm.

2 mg tablet: white, film-coated, oval, biconvex, scored tablet, size 10 mm x 5 mm.

3 mg tablet: white, film-coated, oval, biconvex, scored tablet, size 11 mm x 6.5 mm.

4 mg tablet: white, film-coated, oval, biconvex, scored tablet, size 14 mm x 7.5 mm.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Nodiril tablets are indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent.

Nodiril tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Nodiril tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

## **4.2 Posology and method of administration**

### Method of administration

Oral.

Switching from other antipsychotic medicinal products to risperidone:

It is recommended to discontinue the previous treatment gradually, where medically appropriate, when risperidone treatment is initiated. When switching from depot-antipsychotic medicinal products to risperidone it is recommended to initiate risperidone treatment at the time of the next scheduled injection, if clinically desired.

The need for continuing existing treatment of extrapyramidal symptoms (antiparkinson medication) should be re-evaluated repeatedly.

Adults and adolescents  $\geq 15$  years:

Risperidone can be administered once or twice a day.

The initial dose is 2 mg/day. On the second treatment day the dose may be increased to 4 mg/day.

Thereafter, the dose may be changed individually according to the clinical response. The optimal treatment dose is usually 4-6 mg/day. For some patients slower dose titration and smaller initial and treatment doses may be more suitable.

In clinical trials, doses over 10 mg /day did not increase the antipsychotic effect and they may cause extrapyramidal symptoms. There is no evidence of the safety of doses over 16 mg/day and higher doses than 16 mg/day should not be used.

If further sedation is required, an additional medicinal product (such as a benzodiazepine) should be administered rather than increasing the dose of risperidone.

Elderly:

The recommended initial dose is 0.5 mg two times a day. The dose can be adjusted with 0.5 mg increments to 1 to 2 mg twice daily. Since clinical experience in the elderly is limited, caution should be exercised.

Children and adolescents <15 years:

There is no clinical experience of risperidone treatment with children less than 15 years old.

Therefore it cannot be recommended to use the medicinal product for this patient group.

Hepatic and renal disorders:

For patients with hepatic or renal disorders caution should be exercised, since clinical experience in these patients is limited. The recommended initial dose is 0.25 mg twice daily. According to response the dose may be increased to 1-2 mg twice daily.

The film-coated tablets should be taken with sufficient fluid (e. g. one glass of water), with or without food.

## **4.3 Contraindications**

Hypersensitivity to risperidone or any of the excipients.

## **4.4 Special warnings and special precautions for use**

There is no clinical experience of risperidone treatment in children less than 15 years old. Therefore, this medicine cannot be recommended for group of patients.

Because of the alpha blocking effect of risperidone, orthostatic hypotension may occur especially on initiation of treatment when the dose is increased. Risperidone should be used with caution in patients who suffer from cardiovascular disorders and the dose should be increased gradually (see section 4.2). In case of hypotension a dose decrease should be considered.

Medicinal products that block dopamine receptors may cause tardive dyskinesia. Typical symptoms of tardive dyskinesia include autonomic, rhythmic muscle movements of tongue, mouth and face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If symptoms of tardive dyskinesia occur, discontinuation of antipsychotic treatment should be seriously considered.

During treatment with neuroleptics, neuroleptic malignant syndrome may occur, characterized by hyperthermia, tachypnoea, sweating, muscle rigidity, autonomic instability, altered consciousness, leucocytosis and elevated CPK levels. The occurrence of rhabdomyolysis and renal insufficiency is usually life-threatening. In case of neuroleptic malignant syndrome, the antipsychotic treatment should be discontinued. Besides the initial common supportive measures (external cooling and rehydration), usually anticholinergic medicinal products and benzodiazepines are administered. In severe cases these medicinal products are not sufficiently effective and dantrolene and/or a dopamine agonist should be administered. If this therapy is not effective, or in case of a life threatening situation, electroconvulsive therapy can be life saving.

Paradoxically, antipsychotic medicinal products can increase symptoms like excitation, agitation and aggressiveness. When these symptoms occur, a dose reduction or discontinuation of risperidone treatment may be necessary, just like with other antipsychotic medicinal products.

Special dose recommendations for elderly and hepatic and renal disorder patients are given in section 4.2.

Caution should also be exercised when prescribing risperidone to patients suffering from dementia with Lewy bodies or patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease. The risk of neuroleptic malignant syndrome can also be increased.

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.

Before prescribing risperidone to elderly patients with dementia, the risk/benefit-ratio must be considered, taking into account the risk of cerebrovascular adverse effects among this particular patient population. In clinical studies a threefold increase in cerebrovascular adverse effects, including stroke and transient ischaemic attacks (TIA), was observed (see 4.8). The patient and/or the carer should be required to immediately report symptoms of a potential cerebrovascular episode, such as an abrupt weakness or desensitization of cheeks, upper or lower extremities, or difficulties with speech or disorders of vision. In such an event, all therapeutic possibilities should be considered, including discontinuation of treatment with risperidone. It is therefore recommended not to prescribe risperidone to demented patients with a history of CVA/TIA, hypertension or diabetes.

In the same placebo-controlled studies in elderly patients with dementia, patients treated with furosemide plus risperidone showed a higher incidence of mortality, compared with patients who had received risperidone alone or furosemide alone.

Risperidone should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval and the dose should be gradually titrated. In clinical trials, risperidone was not associated with an increase in QT intervals. As with other antipsychotics, caution is advised when prescribing with medicinal products known to prolong QT interval.

Risperidone should be used with caution in patients with idiopathic hyperprolactinaemia. Special caution should be exercised in patients with possibly prolactin-dependent tumours (e.g. breast cancer).

Hyperglycaemia or exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Patients should be advised of the potential for weight gain.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have rarely been described after abrupt cessation of high doses of antipsychotic medicinal products. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Since the film-coated tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### **4.5 Interaction with other medicinal products and other forms of interactions**

Possible interactions with other medicinal products have not been systematically evaluated. Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting medicinal products.

Antipsychotic medicinal products can increase the effect of alcohol. Therefore, the use of alcohol is not advisable.

The risk of tardive dyskinesia increases when risperidone is taken concomitantly with other antipsychotic medicinal products, lithium, antidepressants, anti-Parkinsonian medication and medicinal products with a central anticholinergic effect. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic metabolite.

The anti- $\alpha_1$ -adrenergic effect can increase the blood pressure lowering effect of phenoxybenzamine, labetalol and other  $\alpha$ -blocking sympathomimetic active substances, also of methyldopa, reserpine and other centrally acting antihypertensive active substances. On the contrary, the blood pressure lowering effect of guanethidine is blocked.

Risperidone may antagonise the effect of levodopa and other dopamine-agonists.

Carbamazepine has been shown to decrease plasma levels of risperidone and its active metabolite. A similar effect might be anticipated with other medicinal products which stimulate metabolizing enzymes in the liver. When carbamazepine treatment or other hepatic enzyme-inducing treatment is interrupted, the dose of risperidone should be re-evaluated and, if necessary, the dose should be decreased.

Quinidine, fluoxetine, paroxetine, terbinafine and other strong inhibitors of CYP2D6 may increase the plasma concentrations of the active moiety. Therefore, the dose of risperidone should be re-evaluated when initiating or discontinuing concomitant treatment with such medicinal products.

Phenothiazines, tricyclic antidepressants and some beta-adrenergic blocking agents may increase plasma concentration of risperidone. Because of the decreased metabolism, the concentration of the active metabolite is consequently lower. Therefore, since the total antipsychotic effect remains unchanged, this interaction is not clinically relevant.

Ranitidine and cimetidine may increase the plasma concentration of risperidone, but the antipsychotic effect is not necessarily increased, because the concentration of the active metabolite is decreased.

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong QT interval (antiarrhythmics class IA or III, antibiotics, medicinal products against malaria, antihistamines) or to cause hypokalaemia or hypomagnesaemia (certain diuretics).

Risperidone does not have a clinically relevant effect on the pharmacokinetics of lithium or valproate.

For interactions with furosemide in elderly subjects with dementia see section 4.4.

During co-administration with other highly protein-bound medicinal products, no clinically relevant displacement of either medicinal product from plasma proteins has been seen.

#### **4.6 Pregnancy and lactation**

##### **Pregnancy**

There are no adequate data from the use of risperidone during pregnancy. Risperidone was not teratogenic in animal studies, but other types of reproductive toxicity were seen (see section 5.3). The use of neuroleptic drugs during the last trimester of pregnancy has resulted in long term but reversible neurological disturbances of extrapyramidal nature in the infant. Risperidone should only be used during pregnancy if the benefit for the mother outweighs the possible risk for the foetus/newborn child.

##### **Lactation**

Risperidone and its active metabolite 9-hydroxy-risperidone are excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses are administered to breast-feeding women. Risperidone should not be used while breast feeding.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effect on the ability to drive and use machines have been performed.

Antipsychotic medicinal products like risperidone can influence the ability to react. Patients should be advised not to drive vehicles or operate machines until the individual reaction to risperidone has been evaluated.

#### 4.8 Undesirable effects

In many cases there have been difficulties when differentiating between adverse effects and symptoms of the disease.

The following adverse reactions have been reported with risperidone

Common: >1/100, < 1/10

Uncommon: >1/1000, < 1/100

Very rare: < 1/10000, including isolated reports

Frequency \ Organ Class	Common	Uncommon	Very rare, including isolated reports
Blood and lymphatic system disorders			A slight decrease in amount of neutrophils and thrombocytes has been reported
Metabolism and nutrition disorders			Hyperglycaemia, exacerbation of pre-existing diabetes
Psychiatric disorders	Agitation, anxiety		
Nervous system disorders	Sleeplessness, headache, sedation <sup>1)</sup>	Drowsiness, fatigue, dizziness, concentration difficulties, extrapyramidal symptoms <sup>2)</sup> : tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia	
Eye disorders		Blurred vision	
Cardiac disorders		Hypotension (also orthostatic hypotension), tachycardia (also reflex tachycardia), orthostatic dizziness or hypertension	
Respiratory, thoracic and mediastinal disorders		Rhinitis	
Gastrointestinal	Weight increase	Constipation,	

disorders		dyspepsia, nausea/vomiting, stomach ache	
Hepato-biliary disorders			Increased hepatic enzyme levels
Skin and subcutaneous tissue disorders		Rash and other allergic reactions	Swelling, pruritus, exanthema, photosensitivity
Musculoskeletal and connective tissue disorders			Muscle weakness
Renal and urinary disorders		Incontinence	
Reproductive system and breast disorders		Priapism, erectile dysfunction, dysfunctional ejaculation, orgasm disturbances	

- 1) Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.
- 2) These symptoms are usually mild and are reversible upon dose reduction and/or administration of anti-Parkinson treatment, if necessary.

*Endocrine disorders:*

Risperidone may lead to dose-related elevation of prolactin levels. Possible associated manifestations are galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and even absence of menstruation (amenorrhoea). In addition, tissue culture studies indicate that cell growth in human breast tumours may be stimulated by prolactin. Although no clear connection between administration of neuroleptics and breast cancer has so far been demonstrated in clinical or epidemiological studies, caution is advisable if there is a relevant previous history.

Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.

Disturbances of the water balance due to overdrinking or disturbances in the secretion of antidiuretic hormone, tardive dyskinesia (see section 4.4), neuroleptic malignant syndrome, disturbances in the body thermoregulation and seizures have been reported during risperidone treatment.

*Cerebrovascular events*

During treatment with risperidone, cerebrovascular events, including cerebrovascular accidents and transient ischaemic attacks (TIA), have been reported. In placebo-controlled studies on elderly patients with dementia, a three-fold increase in the incidence of cerebrovascular adverse events was observed - including strokes (some of which were fatal) and episodes of transient ischaemic attacks (TIA) - in patients treated with risperidone (daily dose of 0.5-2mg), when compared to patients in the placebo group. The relative risk was 2.96 (95 % exact confidence interval: 1.33-7.45). The mean age of this population was 85 years, with ages ranging from 73 to 97 years. The risk was neither linked to the dose, nor to the duration of treatment.

The summarised data from six placebo-controlled clinical trials in elderly patients with dementia (> 65 years) showed an incidence of cerebrovascular events (serious and non-

serious adverse events) in 3.3 % (33/989) of patients treated with risperidone and in 1.2 % (8/693) of patients on placebo (see also 4.4.).

## **4.9 Overdose**

### **Symptoms**

Symptoms of overdose manifest according to known desired and undesired pharmacological effects. The most common symptoms have been fatigue, tachycardia, hypotension and extrapyramidal symptoms. The highest reported overdose of risperidone is 360 mg. According to updated information available, risperidone seems to have a broad safety margin. Following overdose, rare cases of QT-prolongation have been reported. In cases of acute overdose, the possibility of involvement of several medicinal products should be considered.

### **Treatment**

Airways should be kept open and guarantee sufficient supply of oxygen. Gastric lavage (after intubation if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. To be able to diagnose possible arrhythmias, monitoring of heart function should be started immediately and ECG should be monitored constantly.

There is no specific antidote for risperidone. Therefore overdose treatment of risperidone is supportive. Hypotension and possible circulatory collapse should be treated appropriately with intravenous infusion and/or sympathomimetics. If severe extrapyramidal symptoms occur, anticholinergic medicinal products should be given. Careful monitoring should be continued until the patient recovers.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Psycholeptics, antipsychotics

ATC-code: N05AX08

Risperidone is a selective monoaminergic antagonist exhibiting different pharmacological properties from that of traditional neuroleptics. Risperidone binds strongly to both serotonergic 5-HT<sub>2</sub>- and dopaminergic D<sub>2</sub>-receptors. Risperidone also blocks alfa<sub>1</sub>-adenergic receptors and, to a slightly lesser extent, H<sub>1</sub>-histaminergic and alfa<sub>2</sub>-adenergic receptors.

Risperidone has no affinity for cholinergic receptors. Even though risperidone is a strong D<sub>2</sub>-antagonist, which is expected to relieve the positive symptoms of schizophrenia, it causes less induction of catalepsy and reduction in motor activity than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of risperidone to cause extrapyramidal side-effects and broaden risperidone's therapeutic activity towards negative and affective symptoms of schizophrenia.

### **5.2 Pharmacokinetic properties**

#### **Absorption**

Risperidone is totally absorbed after oral administration, reaching the maximum plasma concentration in 1-2 hours. Food has no significant effect on absorption.

In most patients the steady-state concentration of risperidone is reached in one day and that of 9-hydroxyrisperidone in 4-5 days. Within the therapeutic dosage range, the plasma concentration of risperidone increases proportionately with the dose administered.

#### **Distribution**

Risperidone distributes quickly. The volume of distribution is 1-2 l/kg. Risperidone binds to albumin and acid  $\alpha_1$ -glycoprotein in plasma. The plasma protein binding rate for risperidone is 88% and 77% for 9-hydroxyrisperidone.

#### Metabolism

Risperidone is metabolised by the cytochrome P450 2D6 (CYP 2D6) enzyme to 9-hydroxyrisperidone, which has similar pharmacological effects to those of risperidone. Risperidone together with 9-hydroxyrisperidone produces the active antipsychotic effect.

#### Excretion

After oral administration in psychotic patients who are extensive metabolizers, the elimination half-life of risperidone is 3 hours whilst in poor metabolizers the half-life of risperidone is prolonged to 16 hours. The half-life of the active antipsychotic metabolite is 24 hours.

Within one week of oral administration of risperidone, 70% of the dose is excreted in the urine and 14% in the faeces. 35-45% of the dose in the urine is risperidone and 9-hydroxyrisperidone.

#### Special populations

In single-dose studies the plasma concentrations of risperidone were higher than normal and the elimination was slower in elderly patients and in patients with renal impairment.

In patients with hepatic impairment the plasma concentrations were normal.

### 5.3 Preclinical safety data

Repeat-dose toxicity studies in rats and dogs showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. Risperidone was not teratogenic in rats and rabbits. In rats, negative effects were seen on mating behaviour and on the birth weight and survival of the offspring. Moreover, intrauterine exposure to risperidone in rats 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. Risperidone was not genotoxic in a standard battery of tests. In oral carcinogenicity studies in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat) and mammary gland adenocarcinomas (both species) were seen. These tumours can be related to increased prolactin. The relevance of prolactin-derived carcinogenesis in humans is not clear. In vitro and in vivo animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsades de pointes in patients.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Tablet core:

Lactose, anhydrous

Cellulose, microcrystalline

Pregelatinised maize starch

Magnesium stearate

#### Film-coating:

Hypromellose

Macrogol 6000

Titanium dioxide (colorant E 171)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

No special precautions for storage.

## **6.5 Nature and contents of container**

PVC/PVDC/aluminium blister package.

0.5 mg tablets: 6, 6x1, 20, 20x1, 28, 28x1, 30, 30x1, 50, 50x1, 60, 60x1, 98, 98x1, 100, 100x1

1 mg tablets: 6, 6x1, 20, 20x1, 28, 28x1, 30, 30x1, 50, 50x1, 60, 60x1, 98, 98x1, 100, 100x1

2 mg tablets: 6, 6x1, 20, 20x1, 28, 28x1, 30, 30x1, 50, 50x1, 60, 60x1, 98, 98x1, 100, 100x1

3 mg tablets: 6, 6x1, 20, 20x1, 28, 28x1, 30, 30x1, 50, 50x1, 60, 60x1, 98, 98x1, 100, 100x1

4 mg tablets: 6, 6x1, 20, 20x1, 28, 28x1, 30, 30x1, 50, 50x1, 60, 60x1, 98, 98x1, 100, 100x1

Not all pack sizes may be marketed.

## **6.6 Instructions for use and handling and disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Actavis Ltd  
B16, Bulebel Industrial Estate,  
Zejtun ZTN 08  
Malta

## **8. MARKETING AUTHORISATION NUMBER**

0,5 mg tablets: MA245/00301

1 mg tablets: MA245/00302

2 mg tablets: MA245/00303

3 mg tablets: MA245/00304

4 mg tablets: MA245/00305

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

18th October 2005

## **10. DATE OF REVISION OF THE TEXT**