RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG AND 6MG FILM-COATED TABLETS
PL 15922/0046-51

UKPAR

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RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG & 6MG FILM-COATED TABLETS
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LAY SUMMARY

The MHRA granted Apotex Europe Limited Marketing Authorisations (licenses) for the medicinal products Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-Coated Tablets (PL 15922/0046-51). These are prescription-only medicines (POM) 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia.

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets contain the active ingredient risperidone. Risperidone is an antipsychotic drug.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets outweighs the risks, hence Marketing Authorisations have been granted.

The licences for these products were cancelled on 12th June 2007.

RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG & 6MG FILM-COATED TABLETS
PL 15922/0046-51

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets on 20th of December 2006. The products are prescription only medicines.

These applications comprise of complex and standard abridged National Marketing Applications for Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets made under EC Article 10.1 (a) (iii), first paragraph. The proposed legal status is Prescription Only Medicine.

The products contain the active ingredient risperidone and 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.

Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia.

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets contain the active ingredient risperidone. Risperidone is an antipsychotic. Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

These applications for Risperidone were submitted at the same time. The bioequivalence study was sufficient to confirm the bioequivalence of the product to the reference product.

The licences for these products were cancelled on 12th June 2007.

PHARMACEUTICAL ASSESSMENT

Product:	PL 15922/0046 APOTEX EUROPE RISPERIDONE TABLETS 0.5MG
Marketing Authorisation Holder:	APOTEX EUROPE LIMITED
Active Ingredient(s):	RISPERIDONE.
Type of Procedure:	National
Submission Type:	Initial
Submission Category:	Abridged
Submission Complexity:	Standard
E.C. Article:	10.1 (a) (iii)
Legal Status:	POM

GMP Inspection
Satisfactory evidence of GMP has been provided by the applicant for the manufacturing sites and the batch release sites.

1 INTRODUCTION

These national abridged applications (2 complex and 11 standards) for risperidone tablets are made under EC Article 10.1 (a) (iii) of the Directive 2001/83/EC. The applications for all tablet strengths (0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg tablet strengths) are made under first paragraph, so called generic applications claiming essential similarity to the originator products, Risperidal 1mg, 2mg, 3mg and 4mg tablets (PL: 00242/0186 - 0189 first licensed on 08/12/1992). Hence the 10-year rule is complied with.

Risperidone is a novel anti-psychotic drug indicated for use in the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive and/or negative symptoms are prominent.

3.S Drug Substance

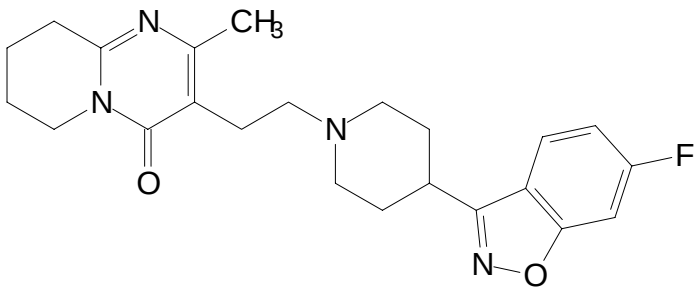
3.2.S.1 General Information

Chemical name: 3-{2-[4[(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-6,7,8-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one

CAS registry number: 106266-06-2

3.2.S.3.1.2 Structure

The structural formula is provided in support of the proposed name. The molecular formula $C_{23}H_{27}FN_4O_2$ is also provided and both are in agreement with the Ph. Eur. monograph for this active substance.



3.2.S.1.3 Physio-Chemical properties

Risperidone with a molecular weight of 410.5, is a white to off-white powder, practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in alcohol. It dissolves in dilute acid solutions. The active substance is the subject of a Ph. Eur. monograph.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

Satisfactory details of the manufacturers have been provided.

3.2.S.3.1 Elucidation of structure & other characteristics

Appropriate evidence of the elucidation of the structure and other characteristics has been provided.

3.2.S.3.2 Impurities

Potential impurities are named which potentially arise from the synthetic process.

Limits for the residual solvents, are considered acceptable.

3.2.S.4 Control of Drug Substance

Appropriate evidence of the control of the drug substance with specification and associated test methods is provided

3.2.S.4.4 Batch Analysis

Batch analyses are provided for batches synthesised at the proposed manufacturing site. Results of batch analyses are satisfactory with respect to the drug substance specification as set by the company.

3.2.S.4.5 Justification for Specification

General statement in support of the assay, related substances and residual solvents methods are provided here with reference to the ICH guidelines and Ph. Eur. monograph and are considered satisfactory.

3.2.S.5 Reference Standards

Satisfactory details of the reference standards used have been provided by the applicant.

3.2.S.6 Container Closure System

Full specifications are provided for the container closure system.

3.2.S.7 Stability

Long term stability data are provided on batches of the active. Storage conditions are 25 °C / 60% RH. Stability protocol provided indicates duration of testing to 60 months at 25 °C and to 6 months at 40 °C.

Currently results are available up to 12 months at real time storage for all three batches. There is little or no change with time and temperature and no stability trends are apparent. A post approval commitment is provided to place one batch of active a year on stability and this is considered satisfactory.

3.2.P Drug Product

3.2.P.1 Description and composition of the drug product

A description of all tablet strengths is provided and is as shown below

Tablet strength	Markings
0.5mg	A red round tablet engraved with “R” on one face and a breakline on the other.
1mg	A white caplet shaped tablet engraved with “R”, a breakline and “1” on one face and plain on the other.
2mg	An orange caplet shaped tablet engraved with “R”, a breakline and “2” on one face and plain on the other.
3mg	A yellow caplet shaped tablet engraved with “R”, a breakline and “3” on one face and plain on the other.
4mg	A green caplet shaped tablet engraved with “R”, a breakline and “4” on one face and plain on the other.
6mg	A yellow caplet shaped tablet engraved with “R”, a breakline and “6” on one face and plain on the other.

In addition to the active substance risperidone, other ingredients included the excipients lactose monohydrate, cellulose microcrystalline, maize starch, colloidal silica, magnesium stearate, opadry white Y-1-7000, hypromellose, red iron oxide E172 (in the 0.5 and 2mg strengths only) and eurolake quinoline yellow E104 (in the 2mg, 3mg, 4mg and 6mg strengths only), indigo carmine lake (4mg only).

3.2.P.2 Pharmaceutical Development

3.2.P.2.1.1-2 Drug Substance and Excipients

Risperidone is a white to off-white solid. The drug substance is practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in alcohol. It dissolved in dilute acid solutions and is the subject of a Ph. Eur. monograph.

A rationale is provided for the choice of the excipients in the final proposed formulation and all excipients had been included in the compatibility test previously carried out. The function of each of the excipients is outlined in the formulation.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Formulation development was carried out with a view to developing a product that was equivalent to the brand leader product Risperdal.

3.2.P.2.3 Manufacturing process development

Satisfactory details have been provided for the manufacturing process development.

3.2.P.3 Manufacture

Satisfactory details of the finished product manufacturer are provided.

3.2.P.3.2 Batch Formula

Batch manufacturing formulas are provided.

3.2.P.3.3 Description of Manufacturing Process & Process Controls

Details are provided as both a narrative and a flow chart of the manufacturing process including the in-process controls. Details of the equipment used at each stage are also specified.

Tablets are then film coated, inspected and packaged into blisters and cartons. Blister packs are subjected to vacuum leak testing.

3.2.P.3.5 Process validation and evaluation

Testing of batches of the blend and batches of the finished product is provided for process validation. All batches of the blend and resulting tablets meet all the specifications as set out for both the common blend and resulting tablets. Batch history is provided, including batch size, date of manufacture is given and batch number of the active drug substance used. Full information is provided about which blend made which particular batch of tablets.

3.2.P.4 Control of excipients

All excipients are Ph. Eur. compendial grade, with the exception of Opadry, iron oxide red, Eurolake quinoline yellow and Eurolake indigo carmine colours. These excipients are controlled to in-house specifications, which have been supplied. Certificates of analysis have been provided for all excipients.

Signed declarations have been provided from all excipient suppliers (bar lactose supplier) confirming that no material of animal or human origin is used in the manufacture of their products. A statement from the supplier of lactose has been provided stating that this is produced from milk obtained from healthy animals under the same conditions as milk for human consumption. This is satisfactory.

3.2.P.5 Control of Drug Product

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

3.2.P.5.2-3 Analytical Procedures & Validation of Analytical Procedures

Appropriate analytical methods and validation of analytical procedures are used by the applicant.

3.2.P.5.4 Batch Analyses

Satisfactory batch analyses are provided for batches, of the 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg.

3.2.P.5.6 Justification of Specification(s)

As currently there is no Ph. Eur. or BP monograph for risperidone tablets, statements are provided to justify the current limits for identification, description and dimension, hardness, average mass, uniformity of mass, related substances, assay, dissolution and microbial testing. Justification of limits and specifications as set is considered satisfactory and in line with batch data supports the tightening of impurity and assay limits.

3.2.P.6 Reference Standards of Materials

Satisfactory details of the reference standards used have been provided by the applicant.

3.2.P.7 Container Closure System

Risperidone tablets are packed in either blister packs composed of PVC/PVdC/Aluminium foil (hard tempered heat-sealable) or HDPE bottles fitted with a polypropylene screw-cap.

Outer pack sizes of blisters are 7, 14, 20, 21, 28, 50, 60 or 100 tablets. The sources and specifications of blister forming materials and bulk packaging are specified and supported by certificates of analysis.

Bottle sizes are specified as either 60ml or 90ml containing either 60 or 100 tablets respectively.

3.2.P.8 Stability

Two sets of stability data is presented for batches of the finished product placed on stability in both packaging types.

Long term data on batches of the active has been provided which would support a retest period of 24 months for this active. A commitment to retest batches immediately prior to use for any active that is used beyond this time point has been provided and this is considered satisfactory

Bioequivalence Studies

Full bioequivalence study is reported. The study is a single dose, randomised, balanced, two-period, 2-treatment, crossover study in healthy volunteers with the following products:

Test (A): 2mg risperidone film coated tablets.
Reference (B): 2mg Risperdal film coated tablets.

The bioequivalence study was carried out using the 2mg strength tablet and this is justified by the applicant on grounds of safety and this is considered satisfactory.

Bioequivalence study was carried out on healthy male and female volunteers using a single dose of the 2mg tablets.

Blood samples were taken as per protocol (25 samples including a pre-dose and post-dose samples over 120 hours). Wash out period – 14 days. Samples were analysed by LC-MS with mass spectrometer detector. The method was validated for between-run and within-run accuracy and precision, recovery, lower limit of quantitation, lower limit of detection, specificity, interference from potentially co-administered drugs, linearity, recovery, dilution integrity, haemolysis effect and stability. Linearity curves have been included in the dossier to support the linearity claims. Sample chromatograms are included in the validation report and are considered satisfactory. A certificate of analysis has been provided for both the risperidone and 9-hydroxy risperidone used in the validation study and are considered satisfactory.

Pharmacokinetic parameters of area under the curve (AUC_{0-t}), from zero to infinity ($AUC_{0-\infty}$) and the observed maximum plasma drug concentration (C_{max}) and time to maximum drug plasma concentration (T_{max}) were determined. Analysis was by ANOVA for statistical treatment for ratio of test/reference and 90% confidence intervals for 24 subjects in the study as per protocol. From the original 28 subjects who entered the study one subject was withdrawn for 4hr post dose vomiting at phase one and one other subject withdrew from the study after period two dosing with no reason recorded.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

	Parent drug Risperidone	Active metabolite 9-OH risperidone
AUC_t	1.05 (0.96 – 1.15)	1.06 (1.00 – 1.12)
AUC_{inf}	1.06 (0.97 – 1.16)	1.08 (1.02 – 1.15)
C_{max}	1.11 (0.98 – 1.25)	1.02 (0.96 – 1.12)
T_{max}	1.0 hrs (both T and R)	4.5 hrs (T), 5.25 hrs (R)

These values are within the accepted regulatory range of 80 – 125% indicating that test is equivalent to the reference in this bioequivalent study for risperidone 2mg film-coated tablets.

VI Module I – Administrative Information

MAA forms

MAA forms are provided for all application and are considered satisfactory.

Part IIC data

Manufacturing process data is considered satisfactory.

1.3 SPC

The proposed SPC is satisfactory.

1.3.3 & 1.3.4 Label & Leaflets

The labels and leaflet are acceptable.

Information about the expert

A pharmacist with 19 years experience in the pharmaceutical industry wrote the pharmaceutical quality overall summary.

VII Module 2

Quality Overall Summary

The report is an overview of the data submitted for the drug product and is generally well written. There is no date on the report. A separate quality overall summary by a chemist, and an employee of the DMF holder is provided with the DMF and is a brief well written summary of the DMF.

VII Pharmaceutical Conclusions

Product Licences for these preparations should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

These national abridged applications are submitted claiming essential similarity to Risperdal (Janssen-Cilag, PL 0242/0347 for the 0.5mg strength), which has been licensed in the UK for more than 10 years.

2. BACKGROUND

Risperidone is well characterised in the literature. It is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives indicated for treatment of acute and chronic schizophrenic psychoses.

3. INDICATIONS

The indications are as follows:

> Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.
>
> Risperidone film-coated tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
>
> Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.
>
> Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

This is acceptable

4. DOSE & DOSE SCHEDULE

> Switching from other anti psychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-parkinson medication should be re-evaluated periodically.
>
> **4.2.a Schizophrenia:**
>
> ***Adults***
>
> Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between

4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

4.2.b Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

The above dose and dose schedule are acceptable

5. TOXICOLOGY

No new data.

6. CLINICAL PHARMACOLOGY

A single bioequivalence study (project 2119) is presented, carried out in compliance with Good Clinical Practice. The multiple strengths exemption criteria are met. In particular pharmacokinetics over the therapeutic range are linear. It is acceptable to use the 2mg strength for tolerability reasons.

This comparative, randomised, two-way, two-period, single dose crossover study compared risperidone 2 mg tablets (Douglas Pharma) and risperdal (France) 2mg tablets. The pharmaceutical assessor confirms that the formulation of the French risperdal is the same as that of the UK risperdal, these are satisfactory test and comparator products.

28 healthy fasted male and female volunteers were randomised to receive 2mg orally of either the applicant's test product or the reference product risperdal. Study products were administered as single dose 1 x 2mg tablets. The randomisation scheme was balanced for sequence and appears random.

Serum drug levels were followed for 5 days following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period between phases was sufficiently long at 14 days.

Log-transformed data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA. T_{max} was analysed non-parametrically.

Of the 28 subjects randomised 2 did not complete the study. In accordance with the protocol only the samples from the first 24 subjects to complete the study were analysed. This is satisfactory.

The appearance of individual plasma concentration – time curves was satisfactory.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

	Parent drug Risperidone	Active metabolite 9-OH risperidone
AUC_t	1.05 (0.96 – 1.15)	1.06 (1.00 – 1.12)
AUC_{inf}	1.06 (0.97 – 1.16)	1.08 (1.02 – 1.15)
C_{max}	1.11 (0.98 – 1.25)	1.07 (1.02 – 1.15)
T_{max}	1.0 hrs (both T and R)	4.5 hrs (T), 5.25 hrs (R)

Assessor's Comment
Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria. Further bioequivalence studies are not required for the 0.5, 1, 3, 4, and 6 mg tablet strengths.

7. EFFICACY
No new data.

8. SAFETY
No new data.

9. EXPERT REPORTS
A satisfactory expert report is provided, by an appropriately qualified individual. It includes a summary of the bioequivalence study and an up to date, well referenced review of the published literature relating to the pharmacology, efficacy and safety of risperidone.

10. PATIENT INFORMATION LEAFLET (PIL)
The PIL is medically satisfactory

11. LABELLING
The labelling is medically satisfactory

12. APPLICATION FORM (MAA)
The MAAs are medically satisfactory.

13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is medically satisfactory

14. DISCUSSION
The application is medically satisfactory. Bioequivalence to the reference product has been shown for all strengths.

15. MEDICAL CONCLUSION
Marketing authorisations may be granted for these preparations.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, 5mg Film-Coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

A bioequivalence study was carried out and the test and reference products shown to be bioequivalent for the appropriate pharmacokinetic criteria.

No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that for the UK reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG & 6MG FILM-COATED TABLETS
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 25/06/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on the 15/07/2004
3	Following assessment of the application the MHRA requested further information on the 14/04/2005, 19/01/2006, 27/06/2006,
4	The applicant responded to the MHRA's requests, providing further information on 28/04/2006, 05/12/2006
5	The application was determined on the 20/12/2006

RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG & 6MG FILM-COATED TABLETS
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
12-06-07	Cancellation	Cancellation of licences	Approved 12-06-07

RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG AND 6MG FILM-COATED TABLETS
PL 15922/0046-51

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 0.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperidone 0.5 mg film-coated tablets containing 0.5 mg risperidone

Excipients: Lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

A red, round film-coated tablet engraved with "R" on one face and a break-line on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Switching from other anti psychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-

parkinson medication should be re-evaluated periodically.

Schizophrenia:

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

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

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 68 years (67-100)

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use.

Irrespective of treatment, dehydration was on overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomized clinical trials conducted in elderly (>65years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with Risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with Risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, a trial fibrillation, etc.

Alpha-blocking acitivityDue to the alpha-blocking activity of Risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

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 QTc intervals. As with other anti psychotics, caution is advised when prescribing with medications known to prolong the QT interval.

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterized by rhythmical involuntary movements, predominantly of

the tongue and/or face. It has been reported that the occurrence of extra pyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all anti psychotic drugs should be considered.

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all anti psychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone tablets. Appropriate clinical monitoring is advisable in diabetic patients and inpatients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

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

As with other anti psychotics, patients should be advised of the potential for weight gain.

A cute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of anti psychotic drugs. 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.

Use of Risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Given the primary CNS effects of Risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the anti psychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolizing enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of Risperidone but not those of the anti psychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of Risperidone but less so of the active anti psychotic fraction.

When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4. (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly received furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of Risperidone from the stomach.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Risperidone in pregnant women. Although Risperidone did not show direct re productive toxicity, some indirect, prolactin-and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats.

The potential risk for humans is unknown.No teratogenic effect of Risperidone was noted in any study.

In animal studies, Risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone had influence on the ability to drive and use machines. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary in continence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with Risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

The incidence and severity of extra pyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extra pyramidal symptoms may occur: tremor, rigidity, hyper salivation, bradykinesia, akathisia, acute dystonia. If a cute in nature, these symptoms are usually mild and are reversible upon dose reduction and /or administration of antiparkinson medication, if necessary.

In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostaticdizziness, hypotension including or thostatic, tachycardia including reflextachycardia and hypertension have been observed following administration of Risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

Hyperglycaemia and exacerbationofpre-existing diabetes have been reported in very rare cases during Risperidone treatment.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of anti diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with anti psychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 OVERDOSE

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of a cute over dosage, the possibility of multiple drug involvement should be considered.

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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. 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 extra pyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AX08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra

pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of Risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of Risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to Risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of Risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and as lower elimination of Risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. There are no pre clinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet-core

Lactose monohydrate

Cellulose microcrystalline

Maize starch

Silica, colloidal anhydrous

Magnesium stearate

Film-coating:

Opadry white Y-1-7000

Hypromellose

Iron Oxide Red (E172)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blisters PVC/PVDC containing 10, 20, 30, 50, 60, 100 film-coated tablets

HDPE Bottles with white polypropylene screw cap containing 30, 60, 100 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Apotex Europe Limited

41 London street

Reading

Berkshire, UK RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)
PL 15922/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/12/2006

10 DATE OF REVISION OF THE TEXT
20/12/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperidone 1 mg film-coated tablets containing 1 mg risperidone

Excipients: Lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

A white caplet shaped film-coated tablet engraved with “R” , a break-line and “1” on one face and plain on the other..

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Switching from other anti psychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-

parkinson medication should be re-evaluated periodically.

Schizophrenia:

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

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

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 68 years (67-100)

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use.

Irrespective of treatment, dehydration was on overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomized clinical trials conducted in elderly (>65years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with Risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with Risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, a trial fibrillation, etc.

Alpha-blocking acitivityDue to the alpha-blocking activity of Risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

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 QTc intervals. As with other anti psychotics, caution is advised when prescribing with medications known to prolong the QT interval.

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extra pyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all anti psychotic drugs should be considered.

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all anti psychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone tablets. Appropriate clinical monitoring is advisable in diabetic patients and inpatients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

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

As with other anti psychotics, patients should be advised of the potential for weight gain.

A cute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of anti psychotic drugs. 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.

Use of Risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Given the primary CNS effects of Risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the anti psychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolizing enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of Risperidone but not those of the anti psychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of Risperidone but less so of the active anti psychotic fraction.

When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active

antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4. (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly received furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of Risperidone from the stomach.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Risperidone in pregnant women. Although Risperidone did not show direct re productive toxicity, some indirect, prolactin-and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats.

The potential risk for humans is unknown.No teratogenic effect of Risperidone was noted in any study.

In animal studies, Risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone had influence on the ability to drive and use machines. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary in continence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with Risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

The incidence and severity of extra pyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extra pyramidal symptoms may occur: tremor, rigidity, hyper salivation, bradykinesia, akathisia, acute dystonia. If a cute in nature, these symptoms are usually mild and are reversible upon dose reduction and /or administration of antiparkinson medication, if necessary.

In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostaticdizziness, hypotension including or thostatic, tachycardia including reflextachycardia and hypertension have been observed following administration of Risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

Hyperglycaemia and exacerbationofpre-existing diabetes have been reported in very rare cases during Risperidone treatment.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of anti diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with anti psychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 OVERDOSE

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of a cute over dosage, the possibility of multiple drug involvement should be considered.

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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. 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 extra pyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AX08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of Risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of Risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to Risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of Risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and as lower elimination of Risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. There are no pre clinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet-core

Lactose monohydrate

Cellulose microcrystalline

Maize starch

Silica, colloidal anhydrous

Magnesium stearate

Film-coating:

Opadry white Y-1-7000

Hypromellose

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blisters PVC/PVDC containing 10, 20, 30, 50, 60, 100 film-coated tablets

HDPE Bottles with white polypropylene screw cap containing 30, 60, 100 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Apotex Europe Limited

41 London street

Reading

Berkshire, UK RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)
PL 15922/0047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/12/2006

10 DATE OF REVISION OF THE TEXT
20/12/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperidone 2 mg film-coated tablets containing 2 mg risperidone

Excipients: Lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

An orange caplet shaped film-coated tablet engraved with “R” , a break-line and “2” on one face and plain on the other

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Switching from other anti psychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-

parkinson medication should be re-evaluated periodically.

Schizophrenia:

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

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

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials

of atypical antipsychotic drugs, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 68 years (67-100)

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use.

Irrespective of treatment, dehydration was on overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomized clinical trials conducted in elderly (>65years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with Risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with Risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, a trial fibrillation, etc.

Alpha-blocking acitivityDue to the alpha-blocking activity of Risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

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 QTc intervals. As with other anti psychotics, caution is advised when prescribing with medications known to prolong the QT interval.

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extra pyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all anti psychotic drugs should be considered.

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all anti psychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone tablets. Appropriate clinical monitoring is advisable in diabetic patients and inpatients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

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

As with other anti psychotics, patients should be advised of the potential for weight gain.

A cute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of anti psychotic drugs. 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.

Use of Risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Given the primary CNS effects of Risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the anti psychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolizing enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of Risperidone but not those of the anti psychotic fraction. Fluoxetine and

paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of Risperidone but less so of the active anti psychotic fraction.

When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4. (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly received furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of Risperidone from the stomach.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Risperidone in pregnant women. Although Risperidone did not show direct re productive toxicity, some indirect, prolactin-and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats.

The potential risk for humans is unknown.No teratogenic effect of Risperidone was noted in any study.

In animal studies, Risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone had influence on the ability to drive and use machines. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary in continence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with Risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

The incidence and severity of extra pyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extra pyramidal symptoms may occur: tremor, rigidity, hyper salivation, bradykinesia, akathisia, acute dystonia. If a cute in nature, these symptoms are usually mild and are reversible upon dose reduction and /or administration of antiparkinson medication, if necessary.

In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostaticdizziness, hypotension including or thostatic, tachycardia including reflextachycardia and hypertension have been observed following administration of Risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

Hyperglycaemia and exacerbationofpre-existing diabetes have been reported in very rare cases during Risperidone treatment.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of anti diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with anti psychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 OVERDOSE

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of a cute over dosage, the possibility of multiple drug involvement should be considered.

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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. 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 extra pyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AX08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of Risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of Risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to Risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of Risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and as lower elimination of Risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. There are no pre clinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet-core

Lactose monohydrate

Cellulose microcrystalline

Maize starch

Silica, colloidal anhydrous

Magnesium stearate

Film-coating:

Opadry white Y-1-7000

Hypromellose

Iron Oxide Red (E172)

Eurolake Quinoline Yellow (E104)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters PVC/PVDC containing 10, 20, 30, 50, 60, 100 film-coated tablets

HDPE Bottles with white polypropylene screw cap containing 30, 60, 100 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Apotex Europe Limited

41 London street

Reading

Berkshire, UK RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)
PL 15922/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/12/2006

10 DATE OF REVISION OF THE TEXT
20/12/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 3 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperidone 3 mg film-coated tablets containing 3 mg risperidone

Excipients: Lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

A yellow caplet shaped film-coated tablet engraved with “R” , a break-line and “3” on one face and plain on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Switching from other anti psychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-

parkinson medication should be re-evaluated periodically.

Schizophrenia:

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should

only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

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

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 68 years (67-100)

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use.

Irrespective of treatment, dehydration was on overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomized clinical trials conducted in elderly (>65years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with Risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with Risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, a trial fibrillation, etc.

Alpha-blocking acitivityDue to the alpha-blocking activity of Risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

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 QTc intervals. As with other anti psychotics, caution is advised when prescribing with medications known to prolong the QT interval.

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extra pyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all anti psychotic drugs should be considered.

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all anti psychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone tablets. Appropriate clinical monitoring is advisable in diabetic patients and inpatients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

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

As with other anti psychotics, patients should be advised of the potential for weight gain.

A cute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of anti psychotic drugs. 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.

Use of Risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Given the primary CNS effects of Risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the anti psychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolizing enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of Risperidone but not those of the anti psychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of Risperidone but less so of the active anti psychotic fraction.

When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4. (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly received furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of Risperidone from the stomach.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Risperidone in pregnant women. Although Risperidone did not show direct re productive toxicity, some indirect, prolactin-and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats.

The potential risk for humans is unknown.No teratogenic effect of Risperidone was noted in any study.

In animal studies, Risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone had influence on the ability to drive and use machines. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary in continence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with Risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

The incidence and severity of extra pyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extra pyramidal symptoms may occur: tremor, rigidity, hyper salivation, bradykinesia, akathisia, acute dystonia. If a cute in nature, these symptoms are usually mild and are reversible upon dose reduction and /or administration of antiparkinson medication, if necessary.

In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostaticdizziness, hypotension including or thostatic, tachycardia including reflextachycardia and hypertension have been observed following administration of Risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

Hyperglycaemia and exacerbationofpre-existing diabetes have been reported in very rare cases during Risperidone treatment.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of anti diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with anti psychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 OVERDOSE

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of a cute over dosage, the possibility of multiple drug involvement should be considered.

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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. 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 extra pyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AX08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of Risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of Risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to Risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of Risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and as lower elimination of Risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. There are no pre clinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet-core

Lactose monohydrate

Cellulose microcrystalline

Maize starch

Silica, colloidal anhydrous

Magnesium stearate

Film-coating:

Opadry white Y-1-7000

Hypromellose

Eurolake Quinoline Yellow (E104)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blisters PVC/PVDC containing 10, 20, 30, 50, 60, 100 film-coated tablets

HDPE Bottles with white polypropylene screw cap containing 30, 60, 100 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited

41 London street

Reading

Berkshire, UK RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)

PL 15922/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/12/2006

10 DATE OF REVISION OF THE TEXT

20/12/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 4 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperidone 4 mg film-coated tablets containing 4 mg risperidone

Excipients: Lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

A green caplet shaped film-coated tablet engraved with “R” , a break-line and “4” on one face and plain on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

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

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 68 years (67-100)

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use.

Irrespective of treatment, dehydration was on overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomized clinical trials conducted in elderly (>65years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with Risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with Risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, a trial fibrillation, etc.

Alpha-blocking acitivityDue to the alpha-blocking activity of Risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

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 QTc intervals. As with other anti psychotics, caution is advised when prescribing with medications known to prolong the QT interval.

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extra pyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all anti psychotic drugs should be considered.

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all anti psychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone tablets. Appropriate clinical monitoring is advisable in

diabetic patients and inpatients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

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

As with other anti psychotics, patients should be advised of the potential for weight gain.

A cute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of anti psychotic drugs. 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.

Use of Risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Given the primary CNS effects of Risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the anti psychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolizing enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of Risperidone but not those of the anti psychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of Risperidone but less so of the active anti psychotic fraction.

When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4. (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly received furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of Risperidone from the stomach.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Risperidone in pregnant women. Although Risperidone did not show direct re productive toxicity, some indirect, prolactin-and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats.

The potential risk for humans is unknown.No teratogenic effect of Risperidone was noted in any study.

In animal studies, Risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone had influence on the ability to drive and use machines. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary in continence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with Risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

The incidence and severity of extra pyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extra pyramidal symptoms may occur: tremor, rigidity, hyper salivation, bradykinesia, akathisia, acute dystonia. If a cute in nature, these symptoms are usually mild and are reversible upon dose reduction and /or administration of antiparkinson medication, if necessary.

In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostaticdizziness, hypotension including or thostatic, tachycardia including reflextachycardia and hypertension have been observed following administration of Risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

Hyperglycaemia and exacerbationofpre-existing diabetes have been reported in very rare cases during Risperidone treatment.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of

inappropriate secretion of anti diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with anti psychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 OVERDOSE

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of a cute over dosage, the possibility of multiple drug involvement should be considered.

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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. 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 extra pyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AX08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to alpha$_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and alpha$_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of Risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of Risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to Risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of Risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and as lower elimination of Risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. There are no pre clinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet-core

Lactose monohydrate
Cellulose microcrystalline
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:

Opadry white Y-1-7000
Hypromellose
Eurolake Indigo Carmine (E132)
Eurolake Quinoline Yellow (E104)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blisters PVC/PVDC containing 10, 20, 30, 50, 60, 100 film-coated tablets

HDPE Bottles with white polypropylene screw cap containing 30, 60, 100 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited

41 London street

Reading

Berkshire, UK RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)

PL 15922/0050

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/12/2006

10 DATE OF REVISION OF THE TEXT

20/12/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 6 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperidone 6 mg film-coated tablets containing 6 mg risperidone

Excipients: Lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

A yellow caplet shaped film-coated tablet engraved with “R” , a break-line and “6” on one face and plain on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Risperidone film-coated 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. Risperidone film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone film-coated tablets are indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Switching from other anti psychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-

parkinson medication should be re-evaluated periodically.

Schizophrenia:

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2mg/day Risperidone. The dosage may be increased to 4mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extra pyramidal symptoms. Doses above10mg/day should only be used in individual patients if the benefit is considered to out weigh the risk. Doses above16mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

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

Children

Risperidone is not recommended for use in children below 15 years due to a lack of data on safety and or efficacy.

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

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

Renal and liver disease

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

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of Risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of Risperidone producing lower plasma levels of the antipsychotic fraction of Risperidone (see Section 4.5). It is therefore not recommended to co-administer Risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of Risperidone.

Method of administration

Oral use.

To be taken with or without food.

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

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 68 years (67-100)

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use.

Irrespective of treatment, dehydration was on overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomized clinical trials conducted in elderly (>65years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with Risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with Risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, a trial fibrillation, etc.

Alpha-blocking acitivityDue to the alpha-blocking activity of Risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

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 QTc intervals. As with other anti psychotics, caution is advised when prescribing with medications known to prolong the QT interval.

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extra pyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all anti psychotic drugs should be considered.

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with

neuroleptics. In this event all anti psychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone tablets. Appropriate clinical monitoring is advisable in diabetic patients and inpatients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

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

As with other anti psychotics, patients should be advised of the potential for weight gain.

A cute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of anti psychotic drugs. 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.

Use of Risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Given the primary CNS effects of Risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the anti psychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolizing enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of Risperidone but not those of the anti psychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of Risperidone but less so of the active anti psychotic fraction.

When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4. (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly received furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of Risperidone from the stomach.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Risperidone in pregnant women. Although Risperidone did not show direct re productive toxicity, some indirect, prolactin-and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats.

The potential risk for humans is unknown.No teratogenic effect of Risperidone was noted in any study.

In animal studies, Risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone had influence on the ability to drive and use machines. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary in continence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with Risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

The incidence and severity of extra pyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extra pyramidal symptoms may occur: tremor, rigidity, hyper salivation, bradykinesia, akathisia, acute dystonia. If a cute in nature, these symptoms are usually mild and are reversible upon dose reduction and /or administration of antiparkinson medication, if necessary.

In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostaticdizziness, hypotension including or thostatic, tachycardia including reflextachycardia and hypertension have been observed following administration of Risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

Hyperglycaemia and exacerbationofpre-existing diabetes have been reported in very rare cases during Risperidone treatment.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of anti diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with anti psychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 OVERDOSE

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of a cute over dosage, the possibility of multiple drug involvement should be considered.

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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. 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 extra pyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AX08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$ adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of Risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of Risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to Risperidone.

This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of Risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and as lower elimination of Risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. There are no pre clinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet-core

Lactose monohydrate

Cellulose microcrystalline

Maize starch

Silica, colloidal anhydrous

Magnesium stearate

Film-coating:

Opadry white Y-1-7000

Hypromellose

Eurolake Quinoline Yellow (E104)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blisters PVC/PVDC containing 10, 20, 30, 50, 60, 100 film-coated tablets

HDPE Bottles with white polypropylene screw cap containing 30, 60, 100 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited

41 London street

Reading

Berkshire, UK RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)
PL 15922/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/12/2006

10 DATE OF REVISION OF THE TEXT
20/12/2006

PACKAGE LEAFLET: INFORMATION FOR THE USER

Risperidone 0,5mg, film-coated tablets
Risperidone 1mg, film-coated tablets
Risperidone 2mg, film-coated tablets
Risperidone 3mg, film-coated tablets
Risperidone 4mg, film-coated tablets
Risperidone 6mg, film-coated tablets

Risperidone

Read this leaflet carefully before you start taking this medicine even if you have only collected a repeat prescription. This leaflet contains information about your medicine. This medicine has been prescribed for you personally and you should NOT pass it on to others. It may harm them, even if their symptoms are the same as yours. You may wish to keep this leaflet as you may want to read it again. If you have further questions, please ask your doctor or your pharmacist.

WHAT IS YOUR MEDICINE?
The active substance in this medicine is Risperidone.
Risperidone tablets have 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg risperidone in them.
The other ingredients are:
Tabletcore: Lactose, colloidal anhydrous silica, maize starch, microcrystalline cellulose (E460), magnesium stearate (E572)
Coating: hypromellose (E464), Opadry white Y-1-7000
The tablets also contain:
Risperidone 0.5mg: Iron Oxide Red (E172).
Risperidone 2mg: Eurolake Quinoline Yellow (E104) and Iron Oxide Red (E172).
Risperidone 3mg: Eurolake Quinoline Yellow (E104).
Risperidone 4mg: Eurolake Quinoline Yellow (E104) and Eurolake Indigo Carmine (E132).
Risperidone 6mg: Eurolake Quinoline Yellow (E104).

Risperidone 0.5mg film-coated tablets:
Red, round film-coated tablets engraved with "R" on one face and a break-line on the other.
Risperidone 1mg film-coated tablets:
White caplet shaped film-coated tablets engraved with "R" , a break-line and "1" on one face and plain on the other.
Risperidone 2mg film-coated tablets:
Orange caplet shaped film-coated tablets engraved with "R" , a break-line and "2" on one face and plain on the other.
Risperidone 3mg film-coated tablets:
Yellow caplet shaped film-coated tablets engraved with "R" , a break-line and "3" on one face and plain on the other.
Risperidone 4mg film-coated tablets:
Green caplet shaped film-coated tablets engraved with "R" , a break-line and "4" on one face and plain on the other.
Risperidone 6mg film-coated tablets:
Yellow caplet shaped film-coated tablets engraved with "R" , a break-line and "6" on one face and plain on the other.

All strengths are available in blister packs of 10, 20, 30, 50, 60, 100 tablets and bottles containing 30, 60, 100 tablets.

Marketing Authorisation Holder:
Apotex Europe Limited, 41 London Street, Reading, Berkshire RG1 4PS, United Kingdom.

Manufacturer responsible for release:
Katwijk B.V., Bio Science Park, Archimedesweg 2-2333; CN Leiden, The Netherlands.

WHAT IS YOUR MEDICINE USED FOR?
Risperidone is one of a group of medicines called antipsychotics. It is used to treat conditions which affect the way you think, feel and/or act. These conditions may cause symptoms such as confusion, hallucinations (eg hearing, seeing or sensing things which are not there), delusions, unusual suspiciousness (paranoia), emotional and social withdrawal. People with these conditions may also feel depressed, guilty, anxious or tense. Risperidone may be taken for both sudden (acute) and long-lasting (chronic) disorders.

In addition, Risperidone may be used to control the symptoms of mania for people with bipolar disorder.

BEFORE YOU TAKE RISPERIDONE TABLETS
Do not take Risperidone if you have ever had an allergic reaction to Risperidone or any of the ingredients listed in the "WHAT IS YOUR MEDICINE?" section above. An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath.
If any of the above applies to you, talk to your doctor and do not take Risperidone.

BEFORE YOU TAKE RISPERIDONE TABLETS YOU SHOULD TELL YOUR DOCTOR IF:
• you suffer from heart or blood vessel disease, liver or kidney disease, Parkinson's disease epilepsy or dementia.
• you are taking medicines for Parkinson's disease.
• you have had a stroke or transient ischaemic attack (temporary reduction in blood flow to the brain).
• you have diabetes or you have a risk of getting diabetes, your doctor may check your blood sugar levels while you are taking Risperidone. (See also section "WHAT UNDESIRABLE EFFECTS DOES YOUR MEDICINE HAVE?").
• you have other risk factors for blood vessel disease, including high blood pressure, diabetes, current smoking or a heart disorder called atrial fibrillation.
• **you use medicines that contain furosemide**. There is a specific risk in elderly people with dementia when Risperidone is used together with medicines that contain furosemide. Furosemide is a diuretic which is used for treatment of high blood pressure and swelling (oedema) due to water retention in the body.

Taking Risperidone while using other medicines
If you are taking any of the following, taking Risperidone as well may make you feel more drowsy:
• Medicines taken for anxiety or to help you to sleep (tranquillisers)
• Certain painkillers
• Some antihistamines (such as chlorpheniramine)
• Certain antidepressants

Only take these medicines while you are on Risperidone if your doctor says that you can:
A drug called carbamazepine, commonly used to treat epilepsy or facial neuralgia (severe pain attacks in the face), or others such as fluoxetine or paroxetine (medicines for treating depression) may affect liver enzymes. This can change the effect of Risperidone.
Please tell your doctor, or pharmacist if you are taking or recently taken any other medicines including medicines obtained without prescription.

Taking Risperidone with food and drink
You should be careful how much alcohol you drink.
The combined effect of Risperidone and alcohol might make you feel drowsy.
Pregnancy and breast feeding
Tell your doctor when you are pregnant, trying to become pregnant, or breast feeding. You should not breast feed if you are taking Risperidone.
Driving and using machines
Taking Risperidone might affect your alertness. Risperidone may cause drowsiness and you may feel dizzy. It is therefore advised not to drive or use potentially dangerous machines Talk to your doctor first before doing so.

HOW TO TAKE YOUR MEDICINE?
Your doctor will decide on the amount of Risperidone you should start with. This may be increased depending on your condition and other medicines you are taking. Always take Risperidone exactly as your doctor has told you. Do not change the amount of medicine you take unless your doctor tells you. Your treatment should be regularly reviewed and changed if appropriate. You should check with your doctor or pharmacist if you are not sure.
• Take Risperidone by mouth only.
• Risperidone tablets can be taken with or without food.
• Swallow the correct number of tablets with some liquid.

The usual dose is:

For adults and adolescents over 15 years of age with conditions which affect the way they think, feel or act:
The dose will be started gradually over the first days of treatment as follows:

Table 1

Day 1: 2 mg	Day 2: 4 mg

This can be taken as a single dose or as half the dose in the morning and half the dose in the evening. However, your doctor may recommend a more gradual increase.
The dosage will then be set to suit your needs but is usually between 4 mg and 6 mg a day. Some patients may require less than 4 mg for a good effect.

For adults and adolescents over 15 years of age with bipolar disorder:
If you need to take Risperidone to help control the symptoms of mania, a starting dose of 2 mg once a day is recommended, and your doctor will adjust this if necessary. Most people feel better with doses between 1 and 6 mg per day. Your doctor will tell you what dose suits your particular situation. Your treatment should be regularly reviewed and changed if appropriate.

Important - never take more than a total of 16 mg per day.

Risperidone is only for those aged 15 years and over.

Elderly and people with liver or kidney disorder
If you are elderly or have a liver or kidney disorder, you should take half the above doses. You will be told how many tablets you need to take.

If you take more Risperidone than you should, talk to a doctor or pharmacist straight away.
The following effects may happen: sedation, drowsiness, rapid heart rate, low blood pressure, muscular rigidity, tremors, and some peculiar, involuntary movements or postures.

Treatment you can take care of before the doctor arrives:
• Take care that the patient is able to breathe (clear the airways).
• Take active coal (available at the pharmacy). This prevents the Risperidone that is still present in the stomach to be taken up by the body.

If you forget to take Risperidone
It is important to take your medicine every day. If you miss a dose in the initial treatment period:
• Take the forgotten dose as soon as possible instead of your next dose.
• Continue to take your doses as prescribed by your doctor.

If you miss a dose after the first few days:
• Do not take the dose you forgot.
• Take your next dose as usual and continue your course.

If you stop taking Risperidone
Do not stop your taking Risperidone without talking to your doctor. It is important that you carry on taking Risperidone for as long as your doctor has told you to.
Risperidone should always be stopped gradually. If you stop taking Risperidone abruptly, you may experience nausea, vomiting, sweating, sleeplessness, muscle stiffness or jerky movements, or your original medical problem may come back. Always follow your doctor's instructions carefully.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

WHAT UNDESIRABLE EFFECTS DOES YOUR MEDICINE HAVE?
Like all medicines, Risperidone can cause side effects, although not everybody gets them.
Sometimes Risperidone may cause side effects such as headache, sleeplessness, anxiety or agitation.
Occasionally the following effects may occur: sleepiness, tiredness, dizziness, difficulty in concentrating, blurred vision, constipation, indigestion, feeling or being sick (nausea or vomiting), stomach ache, sexual potency problems, leakage of urine, runny or blocked nose, liver problems, local skin rash or swelling, or other allergic reactions such as itching, swollen face or lips, or shortness of breath. Weight gain or swelling of the ankles may also occur.
Occasionally strokes or transient ischaemic attacks may occur in people taking Risperidone. If you experience sudden weakness or numbness of the face, arms or legs, especially on one side, or instances of slurred speech, seek medical attention.
In very rare cases, high blood sugar has been reported. See your doctor if you experience symptoms, such as excessive thirst or urination.

If any of these should occur, seek medical attention.

Sometimes trembling, pronounced muscle stiffness or spasm, slowness of movement, excess saliva or restlessness can occur but this will usually disappear if your dose of Risperidone is reduced by your doctor or if your doctor prescribes you an additional medicine.

After prolonged use, women may suffer from milk secretion, an absence of their monthly period or changes in the regularity of their periods. Men may experience breast swelling. If these persist, tell your doctor.

Occasionally, mild blood cell changes have been reported.

In some cases, the blood pressure may fall slightly in the early stages of the treatment, resulting in dizziness. This will usually pass off automatically.
Somewhat later in the treatment, increased blood pressure may also occur, but this is very rare.

In rare cases, Risperidone may cause a desire to drink large amounts of water. You might also experience marked changes in your body temperature or uncontrollable movements, mainly of the face or tongue. Rare cases of convulsions have also occurred. If any of these occurs, contact your doctor as soon as possible.

Very rarely, Risperidone might cause fever, faster breathing, sweating, muscle stiffness and reduced consciousness. If this occurs, stop taking the tablets and contact a doctor at once.
If continuous erection of the penis occurs, contact your doctor immediately
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

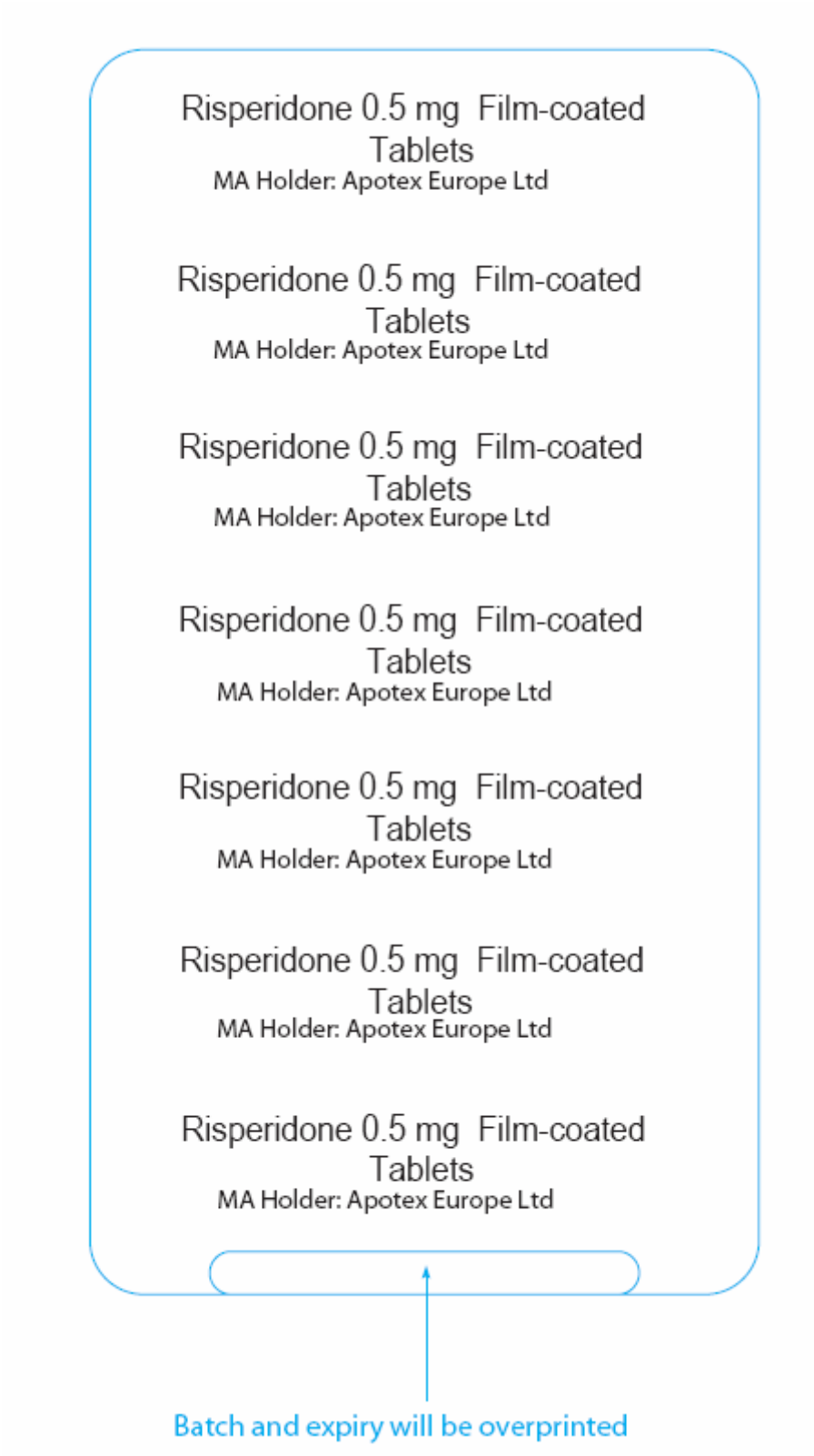
WHERE TO KEEP YOUR MEDICINE?
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
Do not use this medicine after the expiry date stated on the carton.
Store the tablets in the original package. Only remove the tablets when it is time to take your medicine.
Keep the blisters in the outer carton. Do not store the tablets above 30°C.

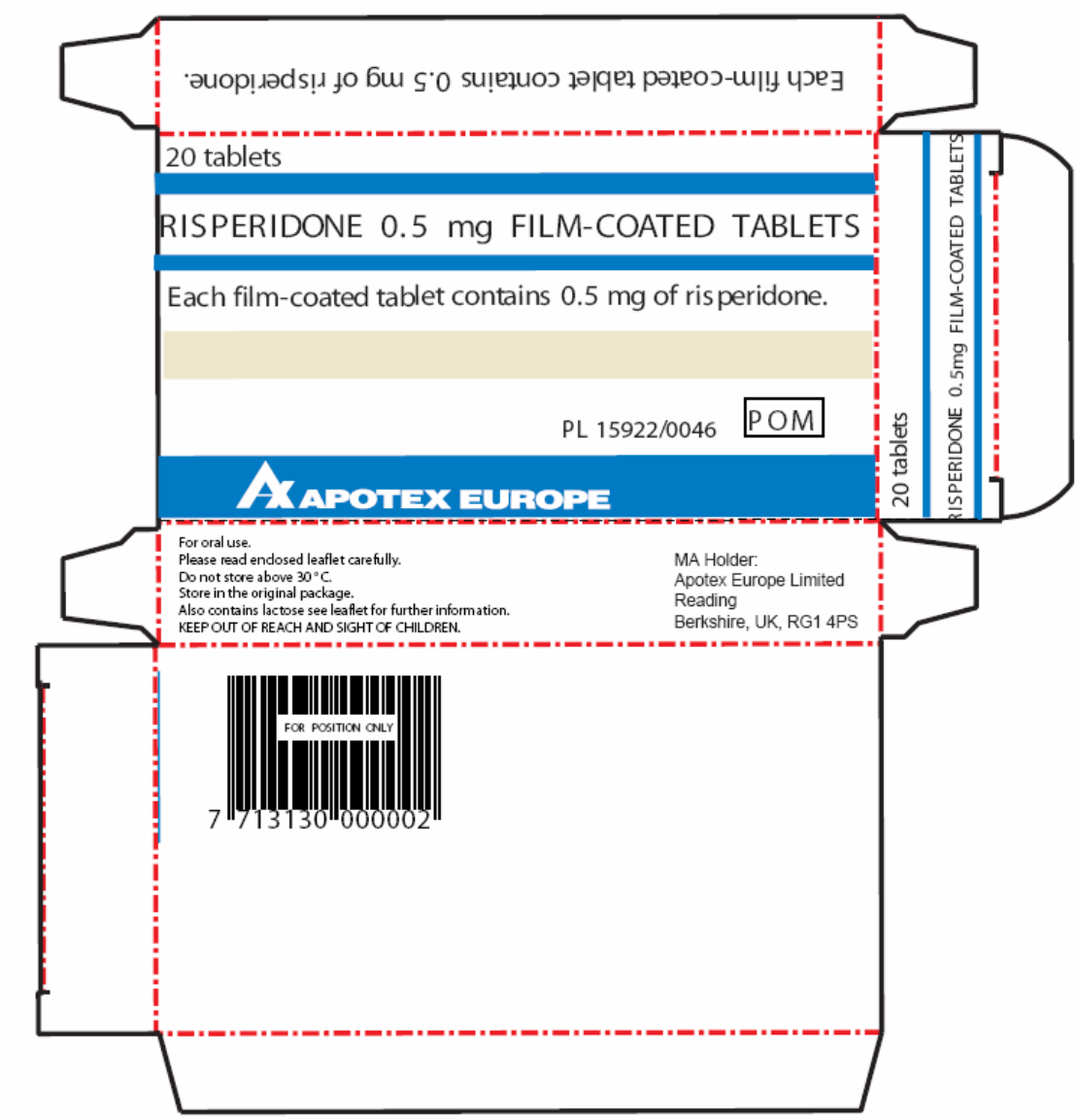
If your doctor decides to stop your treatment, return any left over medicine to the pharmacist. Only keep it if your doctor tells you to.

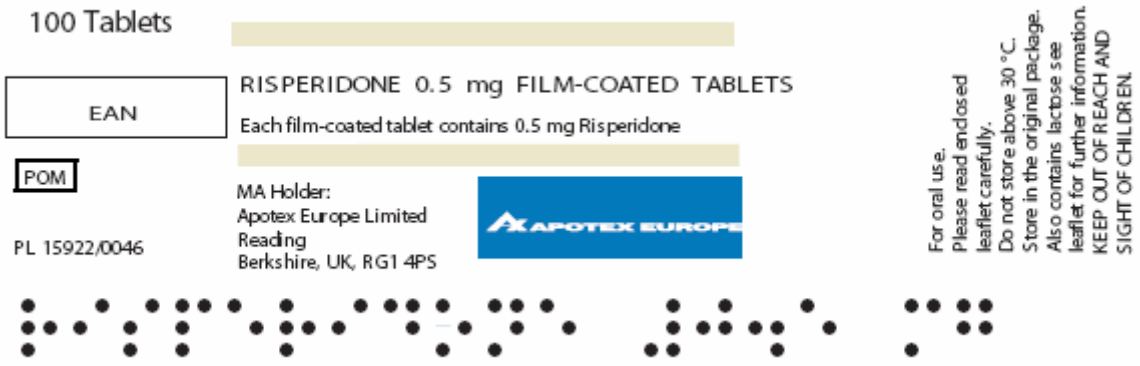
Risperidone 0.5mg film-coated tablets PL 15922/0046
Risperidone 1mg film-coated tablets PL 15922/0047
Risperidone 2mg film-coated tablets PL 15922/0048
Risperidone 3mg film-coated tablets PL 15922/0049
Risperidone 4mg film-coated tablets PL 15922/0050
Risperidone 6mg film-coated tablets PL 15922/0051

Leaflet prepared: December 2006

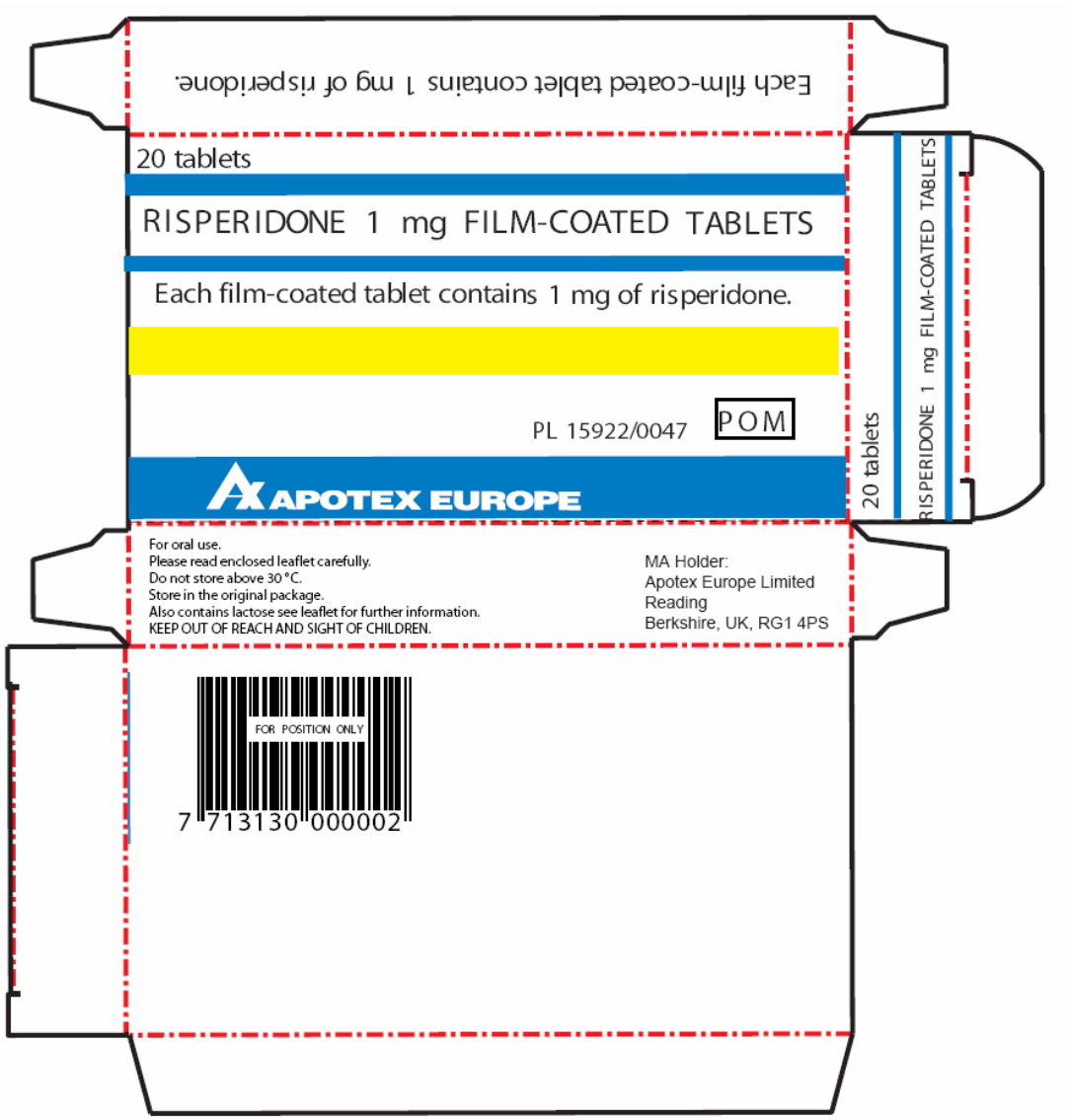
RISPERIDONE 0.5MG FILM-COATED TABLETS
PL 15922/0046




Each film-coated tablet contains 0.5 mg of risperidone.
20 tablets
RISPERIDONE 0.5 mg FILM-COATED TABLETS
Each film-coated tablet contains 0.5 mg of risperidone.
PL 15922/0046
POM
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
FOR POSITION ONLY
7 713130 000002
20 tablets
RISPERIDONE 0.5mg FILM-COATED TABLETS

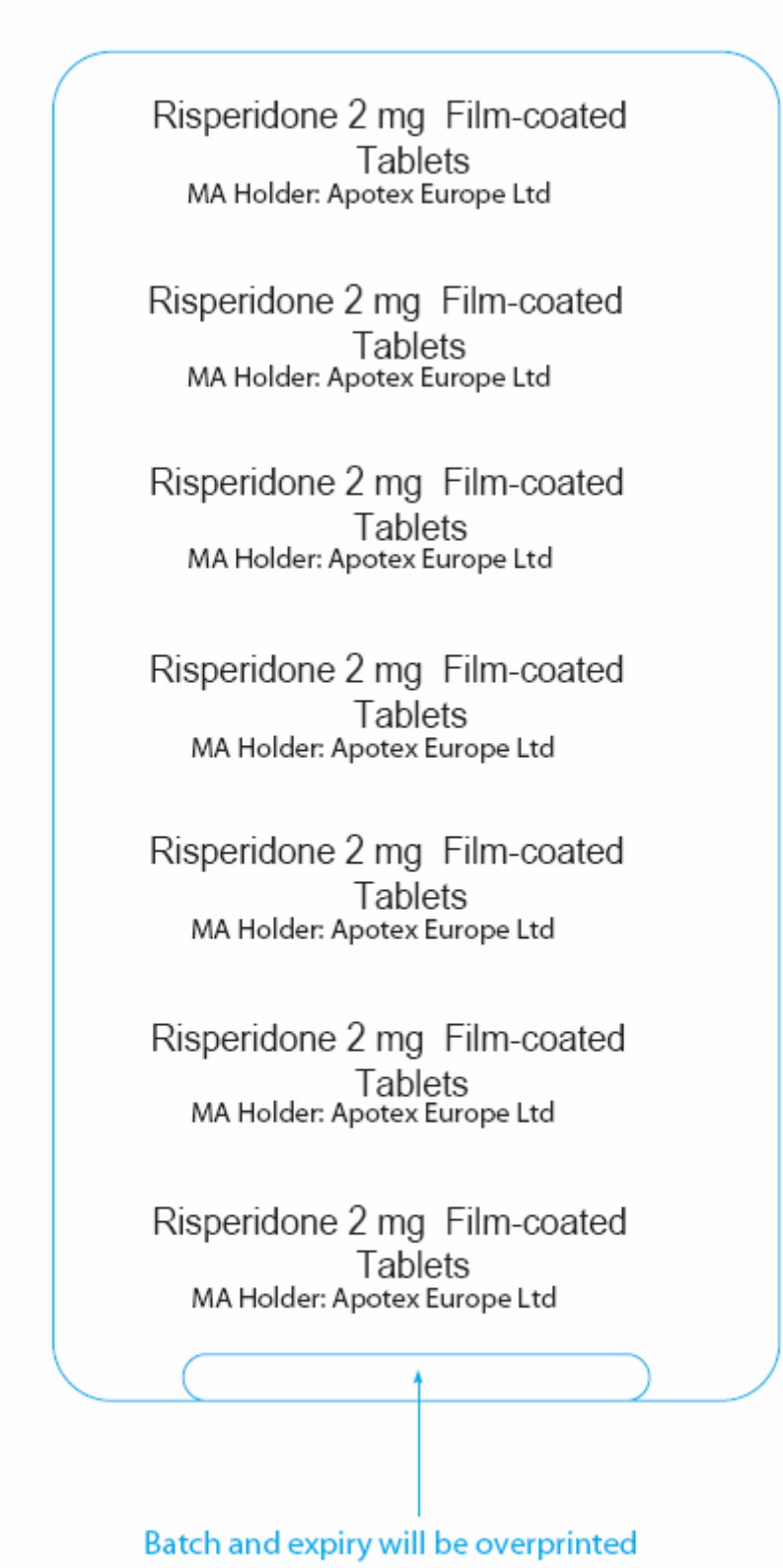

100 Tablets
EAN
RISPERIDONE 0.5 mg FILM-COATED TABLETS
Each film-coated tablet contains 0.5 mg Risperidone
POM
PL 15922/0046
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

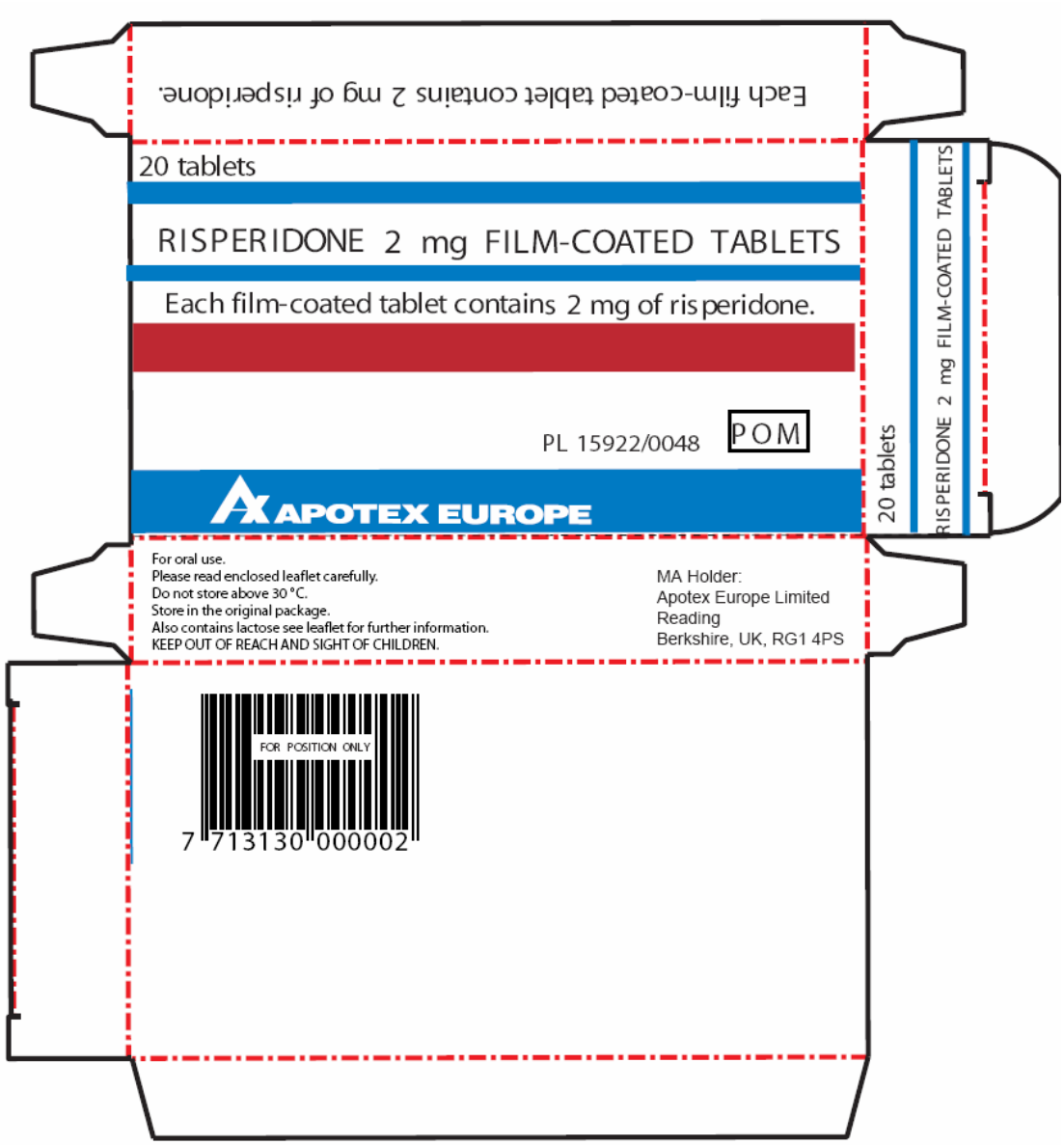
RISPERIDONE 1MG FILM-COATED TABLETS
PL 15922/0047

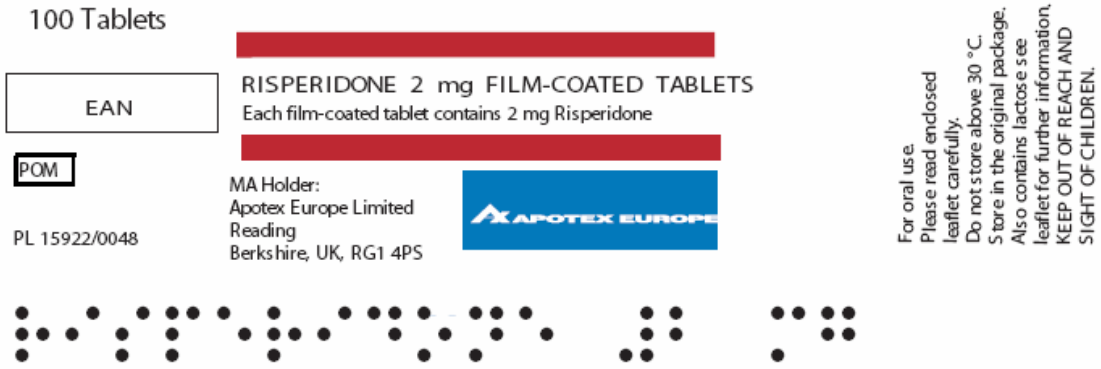

Each film-coated tablet contains 1 mg of risperidone.
20 tablets
RISPERIDONE 1 mg FILM-COATED TABLETS
Each film-coated tablet contains 1 mg of risperidone.
PL 15922/0047
POM
APOTEX EUROPE
20 tablets
RISPERIDONE 1 mg FILM-COATED TABLETS
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
FOR POSITION ONLY
7 713130 000002


100 Tablets
EAN
POM
PL 15922/0047
RISPERIDONE 1 mg FILM-COATED TABLETS
Each film-coated tablet contains 1 mg Risperidone
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

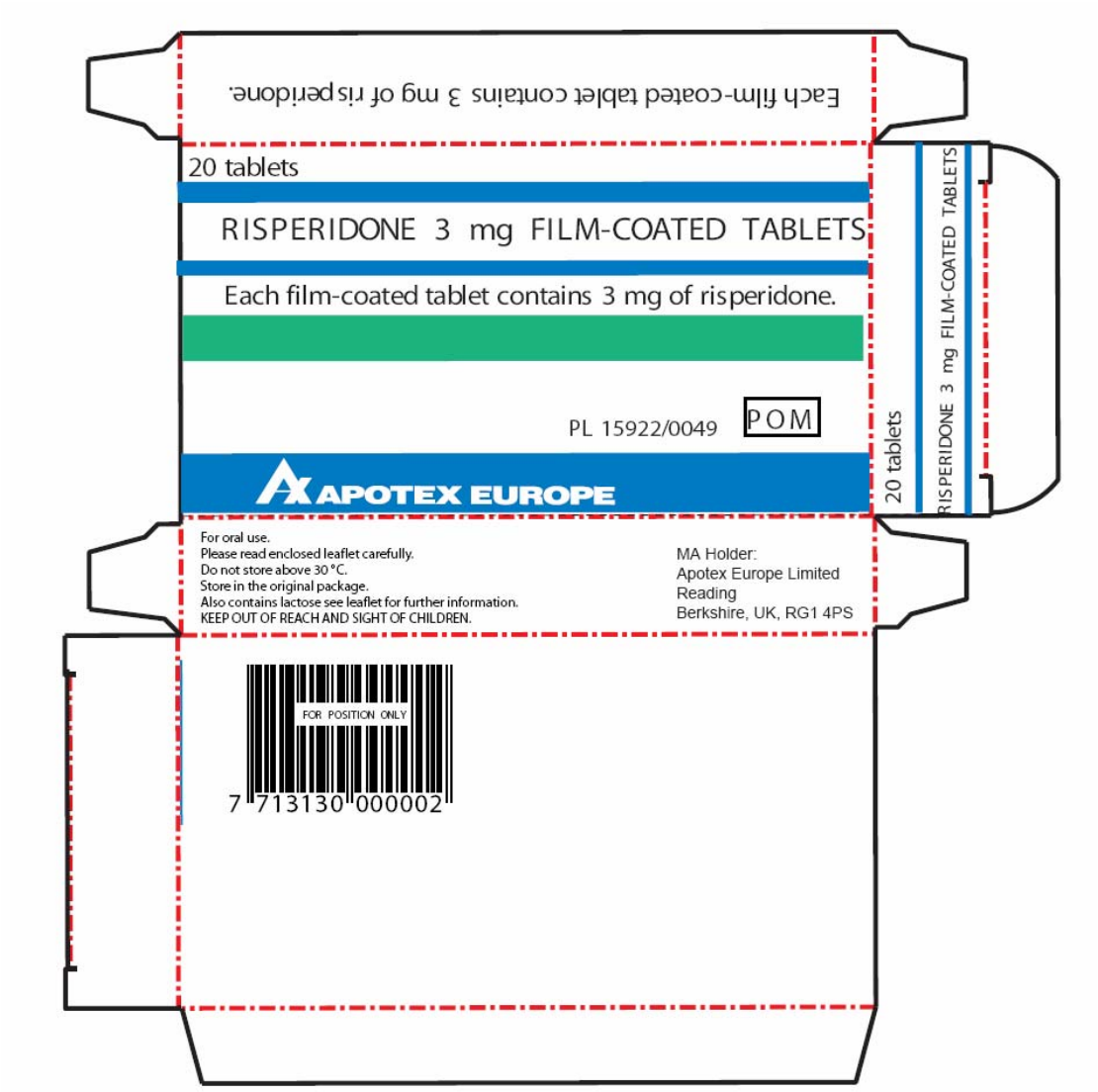
RISPERIDONE 2MG FILM-COATED TABLETS
PL 15922/0048

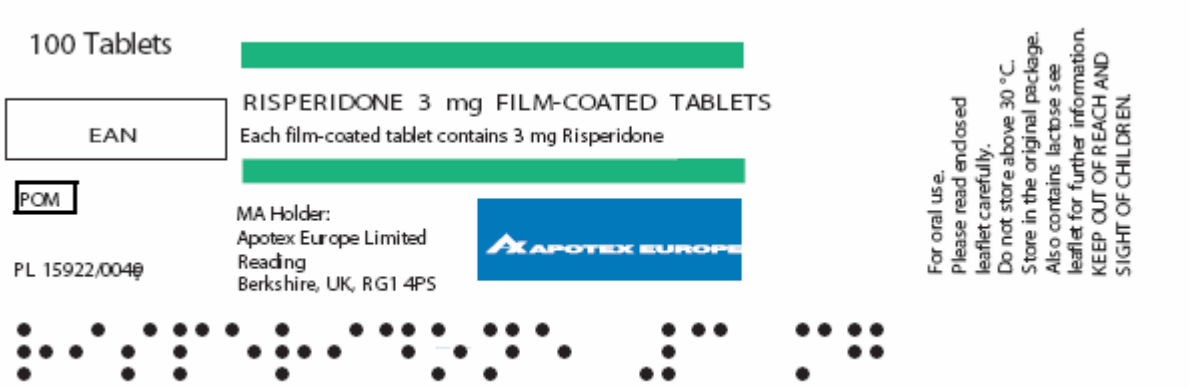



Each film-coated tablet contains 2 mg of risperidone.
20 tablets
RISPERIDONE 2 mg FILM-COATED TABLETS
Each film-coated tablet contains 2 mg of risperidone.
PL 15922/0048
POM
APOTEX EUROPE
20 tablets
RISPERIDONE 2 mg FILM-COATED TABLETS
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
FOR POSITION ONLY
7 713130 000002

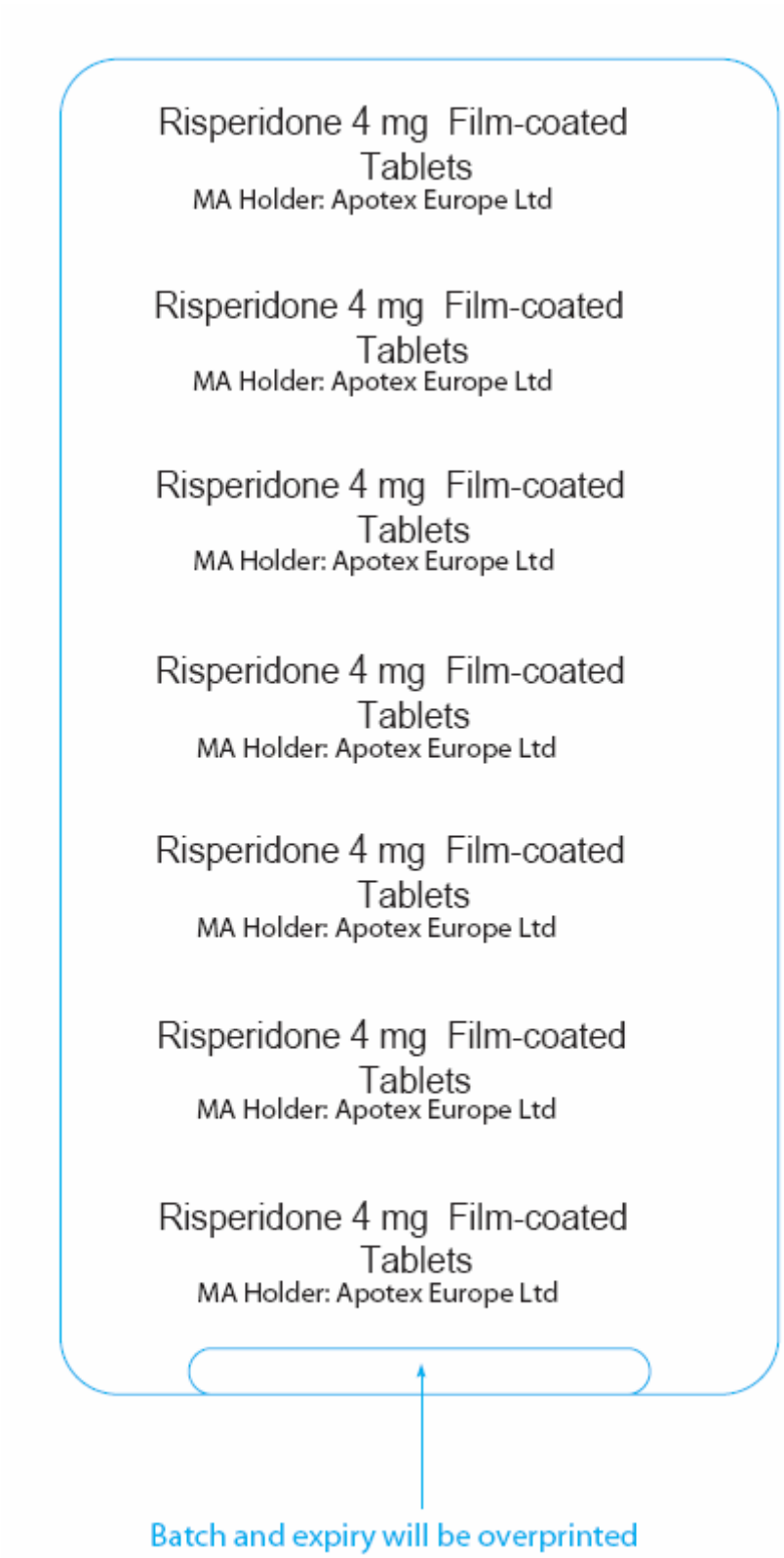

100 Tablets
EAN
POM
PL 15922/0048
RISPERIDONE 2 mg FILM-COATED TABLETS
Each film-coated tablet contains 2 mg Risperidone
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

RISPERIDONE 3MG FILM-COATED TABLETS
PL 15922/0049

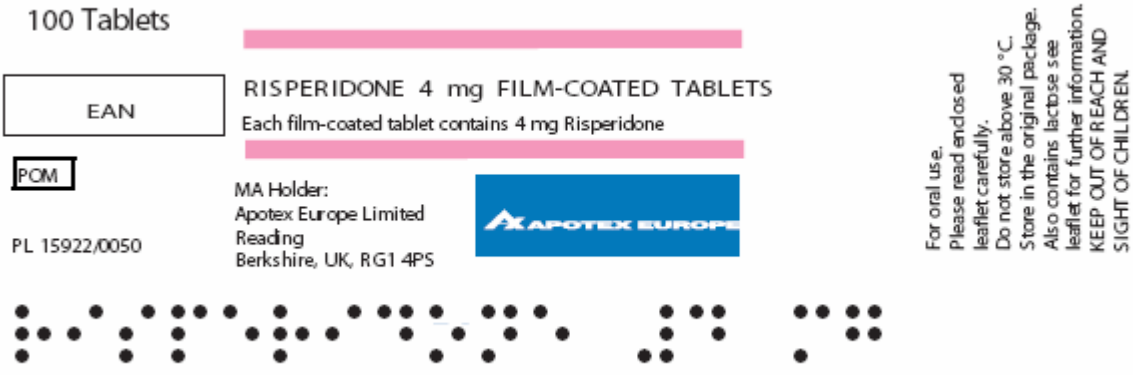

Each film-coated tablet contains 3 mg of risperidone.
20 tablets
RISPERIDONE 3 mg FILM-COATED TABLETS
Each film-coated tablet contains 3 mg of risperidone.
PL 15922/0049
POM
APOTEX EUROPE
20 tablets
RISPERIDONE 3 mg FILM-COATED TABLETS
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
FOR POSITION ONLY
7 713130 000002


100 Tablets
EAN
POM
PL 15922/0049
RISPERIDONE 3 mg FILM-COATED TABLETS
Each film-coated tablet contains 3 mg Risperidone
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

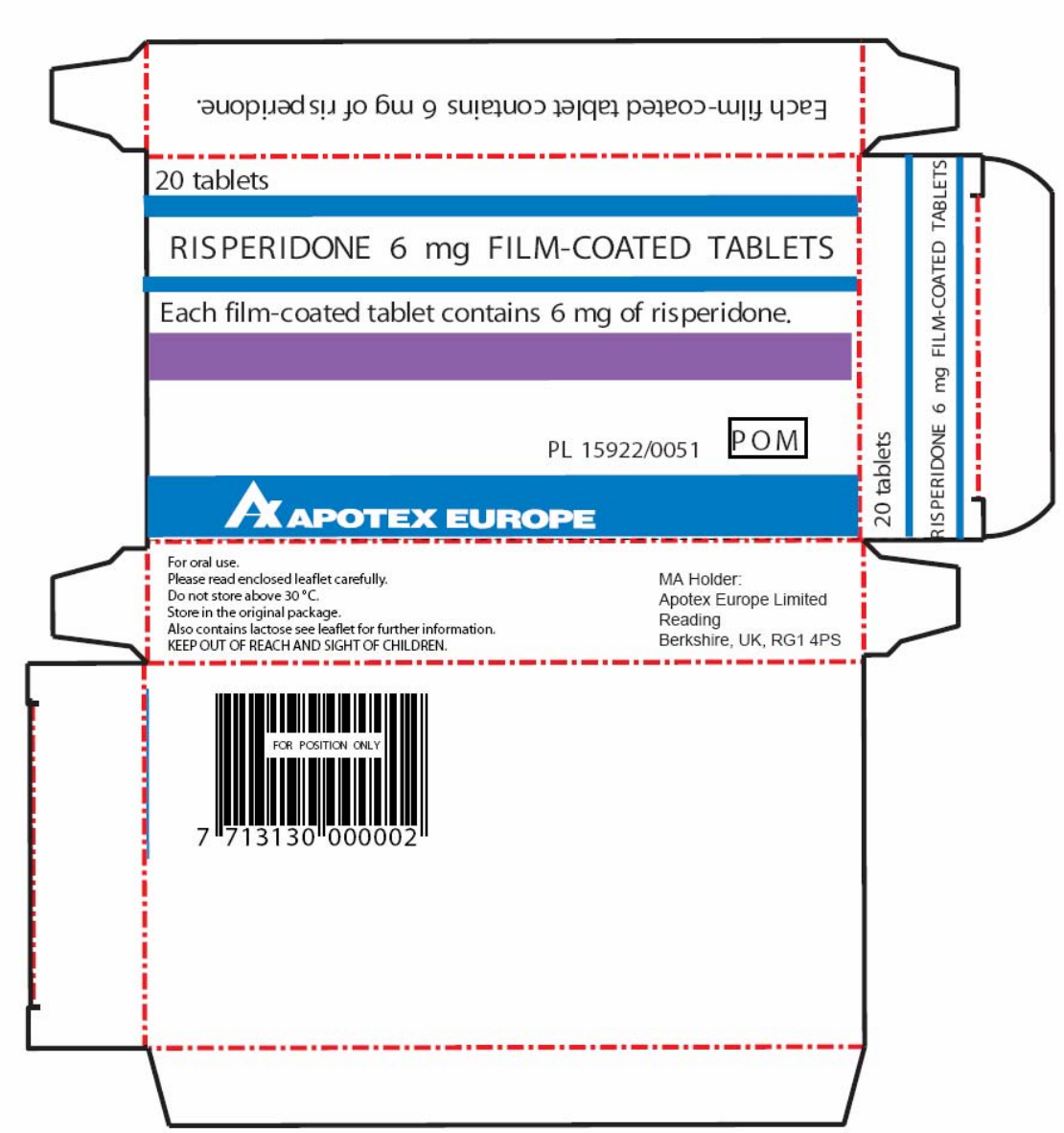
RISPERIDONE 4MG FILM-COATED TABLETS
PL 15922/0050

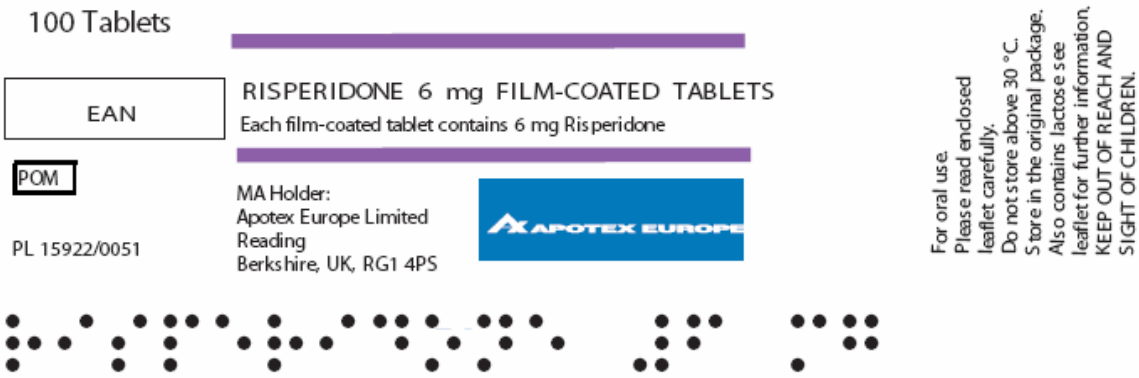



Each film-coated tablet contains 4 mg of risperidone.
20 tablets
RISPERIDONE 4 mg FILM-COATED TABLETS
Each film-coated tablet contains 4 mg of risperidone.
PL 15922/0050
POM
APOTEX EUROPE
20 tablets
RISPERIDONE 4 mg FILM-COATED TABLETS
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
FOR POSITION ONLY
7 713130 000002


100 Tablets
EAN
RISPERIDONE 4 mg FILM-COATED TABLETS
Each film-coated tablet contains 4 mg Risperidone
POM
PL 15922/0050
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

RISPERIDONE 6MG FILM-COATED TABLETS
PL 15922/0051


Each film-coated tablet contains 6 mg of risperidone.
20 tablets
RISPERIDONE 6 mg FILM-COATED TABLETS
Each film-coated tablet contains 6 mg of risperidone.
PL 15922/0051
POM
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
FOR POSITION ONLY
7 713130 000002
20 tablets
RISPERIDONE 6 mg FILM-COATED TABLETS


100 Tablets
EAN
RISPERIDONE 6 mg FILM-COATED TABLETS
Each film-coated tablet contains 6 mg Risperidone
POM
PL 15922/0051
MA Holder:
Apotex Europe Limited
Reading
Berkshire, UK, RG1 4PS
APOTEX EUROPE
For oral use.
Please read enclosed leaflet carefully.
Do not store above 30 °C.
Store in the original package.
Also contains lactose see leaflet for further information.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.