Safeguarding public health

MHRA

Public Assessment Report

Mirtazapine 15mg Tablets
PL 20532/0018

Mirtazapine 30mg Tablets
PL 20532/0019

Mirtazapine 45mg Tablets
PL 20532/0020

Medicines and Healthcare products Regulatory Agency

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

MIRTAZAPINE 30MG TABLETS
PL 20532/0019

MIRTAZAPINE 45MG TABLETS
PL 20532/0020

UKPAR

TABLE OF CONTENTS

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

MIRTAZAPINE 30MG TABLETS
PL 20532/0019

MIRTAZAPINE 45MG TABLETS
PL 20532/0020

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products Mirtazapine 15mg, 30mg and 45mg Tablets (PLs 20532/0018-20). These are prescription only medicines [POMs] used for the treatment of depression.

These products contain the active substance mirtazapine.

The clinical data presented to the MHRA, before licensing, demonstrated that Mirtazapine 15mg, 30mg and 45mg Tablets are essentially similar or equivalent to the approved products, Zispin (Mirtazapine) 15mg, 30mg and 45mg Tablets, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Mirtazapine 15mg, 30mg and 45mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

MIRTAZAPINE 30MG TABLETS
PL 20532/0019

MIRTAZAPINE 45MG TABLETS
PL 20532/0020

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Mirtazapine 15mg, 30mg and 45mg Tablets (PLs 20532/0018-20) to Sandoz Limited on 31 July 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Zispin (Mirtazapine) 15mg, 30mg and 45mg Tablets.

These products contain the active ingredient mirtazapine and are indicated for the treatment of depressive illness.

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

PHARMACEUTICAL ASSESSMENT

PL Number: **PLs 20532/0018-20**
Name of Product: **Mirtazapine 15mg, 30mg and 45mg Tablets**
Active (s): **Mirtazapine**
Company Name: **Aurobindo Pharma Limited**
E.C. Article: **10.1(a)(iii)**
Legal Status: **POM**

INTRODUCTION

Legal Basis

These are national applications for 3 strengths of mirtazapine tablets: 15mg, 30mg and 45mg. These abridged applications were submitted under article 10.1(a)(iii) of Directive 2001/83/EC, citing Zispin (Mirtazapine) 30mg Tablets (Organon Laboratories Ltd – PL 00065/0145) as the UK reference product. The original products cited are Remeron (Mirtazapine) 15mg, 30mg and 45mg tablets, licensed in the Netherlands since 1994.

Use

Mirtazapine is an anti-depressant and is indicated for the treatment of depression. The claimed indications "Treatment of depressive illness" are consistent with those licensed in the cross-referenced product.

Background

Details of the reference products are found below.

PL Number	Tablet strength	Granted
PL 00065/0144	Mirtazapine 15mg Tablets	4 July 1997
PL 00065/0145	Mirtazapine 30mg Tablets	4 July 1997
PL 00065/0157	Mirtazapine 45mg Tablets	13 January 2000

DRUG SUBSTANCE

General information

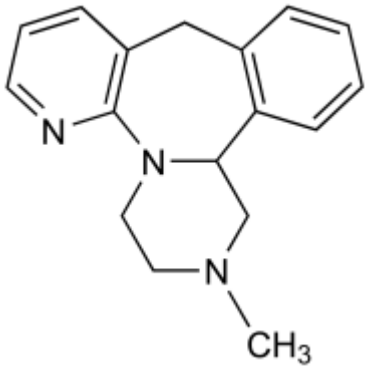
Nomenclature

1,2,3,4,10,14b-Hexahydro–2–methylpyrazino[2,1-a]pyrido[2,3-c][2]-benzazepine

$C_{17}H_{19}N_3$=265.36

CAS—61337–67–5

Structure



General properties

White to creamy-white crystalline powder

Freely soluble in methanol and in dichloromethane

Melting point 114-117°C

Specific optical rotation -0.5º to +0.5º

Manufacture

Manufacturer

A suitable manufacturing site has been named.

Description of manufacturing process

A satisfactory description of the manufacturing process is provided.

Control of materials

A statement is provided that materials used are not derived from animals which are susceptible to TSE. The starting material is satisfactorily controlled by a suitable specification.

Satisfactory specifications are also provided for all reagents.

Characterisation

The active substance has been characterised by suitable methods.

Elucidation of structure and other characteristics

Isomerism
Mirtazapine shows optical isomerism and the compound is commercially available as the racemic mixture (+0.5°C to – 0.5ºC).

Mitazapine is soluble in methanol and dichloromethane and practically insoluble in water, but its solubility increases with increasing acidity.

Impurities

Details of impurities are provided.

Control of drug substance

Specification

The drug substance specification provided is acceptable.

Analytical procedures
Validation of analytical procedures

Satisfactory details are provided.

Batch analysis

Batch analysis data show compliance with the specification.

Reference standards or materials

The reference batch number, Certificates of Analysis and proof of structure data are provided.

DRUG PRODUCT

Description and composition of the drug product

Ingredients		**Function of ingredients**
Core ingredients		
Mirtazapine	HSE	Active
Lactose monohydrate	Ph.Eur.	Diluent
Hydroxypropylcellulose	Ph.Eur.	Binder
Maize starch	Ph.Eur.	Disintegrant
Silica, colloidal anhydrous	Ph.Eur.	Glidant
Low-substituted hydroxypropyl cellulose	USNF	Disintegrant
Magnesium Stearate	Ph.Eur.	Lubricant
Coating ingredients		
Opadry White 20A58806	HSE	Coating material
Opadry Yellow 20A52560	HSE	Coating material
Opadry Brown 20A56788	HSE	Coating material

Pharmaceutical development

Mirtazapine is rapidly and completely absorbed after oral administration from the gastro–intestinal tract. Peak plasma levels are reached after about 2 hours. Steady state is reached after 3 to 4 days. Linear pharmacokinetics are displayed within the recommended dose range.

Food intake has no influence on the pharmacokinetics. It is extensively metabolised in the liver and eliminated in urine (75%) and faeces (15%) within a few days. Metabolism occurs by the P450 cytochrome oxidase pathway into four metabolites via demethylation and hydroxylation followed by glucuronide conjugation. Cytochrome 2D6 and 1A2 are involved in the formation of 8–hydroxy metabolite and 3A in the N-desmethyl (active) and N-oxide metabolites. Elimination of the parent compound occurs via hepatic metabolism with demethylation and oxidation with subsequent conjugation of the metabolites. The bioavailability of mirtazapine is 50% and half life about 20-40 hours. It is 85% plasma bound. (Clarke's Analysis of Drugs and Poisons 2004).

Mirtazapine's absorption is not influenced by food (Martindale).

Essential similarity
The active is the same. The impurity profile of the proposed product is comparable to that of the reference product. The pharmaceutical form is the same and both use the oral route. Bioequivalence has been demonstrated.

Dose proportionality of the different strengths
Tablets are made at the same site by the same method. They have similar dissolution profiles. They contain the same excipients in the same proportions. The pharmacokinetics are linear over the recommended dosage range (Clarke's Analysis of Drugs and Poisons 2004).

Container closure system

Blisters – White Opaque 250µm PVC coated with 60gm PVdC and 25µm aluminium foil with heat seal lacquer. Both plastic and aluminium foils comply with Ph.Eur. requirements and are food grade materials. The plastic layer complies with European Directives EU/1991/91/EC, EU/78/142/EC and EU/94/62/EEC.

Microbial testing

Microbial testing in accordance with the Ph.Eur. is performed on the finished product.

Manufacture

The manufacturing site has been inspected by the MHRA and accepted as a suitable site to be named on UK licences.

Description of manufacturing process and process controls

Full details provided.

Process validation and/or evaluation

Satisfactory details provided.

Control of excipients

Specifications

The following excipients comply with the Ph.Eur.:

Lactose monohydrate
Hydroxypropylcellulose
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Low substituted hydroxypropyl cellulose is controlled by USNF monograph.

Opadry coatings are controlled by satisfactory in-house specifications. Ingredients of the coating are of pharmacopoeial quality.

Analytical procedures

Satisfactory details of analytical procedures are presented.

Justification of specifications

Certificates of Analysis demonstrating compliance with the specifications are provided.

Excipients of human or animal origin

All excipients are derived from vegetable sources except lactose monohydrate, which is derived from healthy animals.

Control of drug product

Specification

A suitable finished product specification is provided.

Analytical procedures

Analytical procedures are adequately described.

Validation of analytical procedures

Satisfactory details are provided.

Batch analysis

The batch analysis confirms compliance with the finished product specification.

Justification of specification

Appropriate justifications have been provided.

Reference standards or materials

Certificates of Analysis for the reference standards and impurities have been provided.

Container closure system

Satisfactory Certificates of Analysis are presented. The aluminium foil is certified as complying with 94/62/EEC and 78/142/EEC (vinyl monomers) and 2002/72/EC.

Stability

Stability summary and conclusions

A shelf life of 3 years with no special storage conditions has been requested. This is acceptable.

Stability data

Satisfactory data at 40ºC and 25ºC are provided.

Little change is noted in any of the parameters measured. As there are no out-of-specification results at either accelerated or normal conditions, this is accepted.

MODULE 5

See Clinical Assessment Report.

SUMMARY OF PRODUCT CHARACTERISTICS
LABELLING
PATIENT INFORMATION LEAFLET

Satisfactory.

PRECLINICAL ASSESSMENT

PL Number:	**PLs 20532/0018-20**
Name of Product:	**Mirtazapine 15mg, 30mg and 45mg Tablets**
Active (s):	**Mirtazapine**
Company Name:	**Aurobindo Pharma Limited**
E.C. Article:	**10.1(a)(iii)**
Legal Status:	**POM**

INTRODUCTION

These are national applications for 3 strengths of mirtazapine tablets: 15mg, 30mg and 45mg. These abridged applications are submitted under Article 10.1(a)(iii) of Directive 2001/83/EC, citing Zispin (Mirtazapine) 30mg Tablets (Organon Laboratories Ltd – PL 00065/0145) as the UK reference product. The original products cited are Remeron (Mirtazapine) 15mg, 30mg and 45mg tablets, licensed in the Netherlands since 1994.

The proposed indication is "treatment of depressive illness".

GLP ASPECTS

No non-clinical data are submitted.

PHARMACODYNAMICS / PHARMACOKINETICS

Mirtazapine enhances central noradrenergic and serotonergic activity. Both enantiomers are thought to contribute to its antidepressant activity. The S(+) enantiomer blocks α_2 adrenoceptors and 5-HT_2 receptors, which may account for its anxiolytic and sleep improving properties, while the R(-) enantiomer blocks 5-HT_3 receptors. Mirtazapine is reported to enhance 5-HT_1 receptor mediated transmission. It is also a potent histamine H_1 receptor antagonist, which may explain its sedative properties.

In man, mirtazapine is well absorbed from the gastrointestinal tract with peak plasma levels occurring after about 2 hours. Plasma protein binding is about 85%. Mirtazapine is extensively metabolised in the liver and the major biotransformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The N-desmethyl metabolite is pharmacologically active. Elimination is via urine (75%) and faeces (15%). The mean plasma elimination half-life is 20 to 40 hours.

Data from animal studies indicate that mirtazapine crosses the placenta and is distributed into breast milk.

Assessor's overall conclusion on pharmacodynamics / pharmacokinetics

The pharmacology of mirtazapine is well established and the applicant has not supplied any new preclinical pharmacology data.

SPC sections 5.1 and 5.2 are consistent with those of the UK reference product and, from a preclinical point of view, are satisfactory.

TOXICOLOGY

The applicant has not submitted any relevant information. Previous mirtazapine assessment reports indicate that preclinical toxicology studies with mirtazapine revealed no findings of particular concern.

Studies on impurities (essential similarity)

There are no impurities issues.

Ecotoxicity/Environmental risk

No environmental risk assessment is required for an application of this type.

Assessor's overall conclusions on toxicology

There are no particular non-clinical concerns with this drug. Furthermore, there is considerable clinical experience with mirtazapine and this would, in any case, override nonclinical concerns.

Sections 4.6 and 5.3 of the SPCs are consistent with those of the cross-referenced product.

CLINICAL ASSESSMENT

PL Number:	**PLs 20532/0018-20**
Name of Product:	**Mirtazapine 15mg, 30mg and 45mg Tablets**
Active (s):	**Mirtazapine**
Company Name:	**Aurobindo Pharma Limited**
E.C. Article:	**10.1(a)(iii)**
Legal Status:	**POM**

INTRODUCTION

These are mainstream, national, abridged standard licensing applications submitted under Article 10.1(a)(iii), Directive 2001/83 EC as amended. The applicant has claimed essential similarity to Zispin (Mirtazapine) 30mg Tablets (PL 00065/0145, Marketing Authorisation Holder: Organon Laboratories Ltd). Mirtazapine was first licensed in the EU in the Netherlands in 1994. In the UK marketing authorization was granted on 4 July 1997.

BACKGROUND

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. It is related to tricyclic antidepressants. It is a presynaptic alpha$_2$-antagonist, increases central noradrenergic and serotonergic neurotransmission. It is claimed to have few antimascurinic effects, but causes sedation during initial treatment. It is said to be more effective in the presence of symptoms such as psychomotor inhibition, sleep disturbances (early wakening) and weight loss.

INDICATION

Treatment of depressive illness.

Assessor's comment

This is consistent with the indication of the reference product.

DOSE AND DOSE SCHEDULE

These are in line with those of the reference product.

TOXICOLOGY

No new data are provided or required. However, the applicant has submitted a Preclinical Expert Report.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mirtazapine is a centrally active presynaptic alpha$_2$-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-hydroxytryptamine$_1$ (5-HT$_1$) receptors because 5-HT$_2$ and 5-HT$_3$ receptors are blocked by mirtazapine.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

Pharmacokinetics

Following oral administration, mirtazapine is rapidly absorbed, reaching peak plasma levels after about two hours. It has a bioavailability of approximately 50%. Binding of mirtazapine to plasma proteins is about 85%. The mean elimination half-life is 20-40 hours. Steady state is reached following 3-4 days of dosing; after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

Mirtazapine is extensively metabolised and eliminated via urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

Bioequivalence

The applicant has submitted the results of a comparative pharmacokinetic study. The study compared the plasma profiles which resulted from administration of 30mg mirtazapine Tablets (Test) and 30mg Zispin 30mg Tablets (Reference).

The subjects were 24 healthy male volunteers (aged 18-50 years), who were studied in a single-dose, fasting, randomised, open, two-way crossover study, with a two-week washout period between the study periods. Blood samples were obtained for up to 72 hours after each dose, and individual mirtazapine plasma levels were determined by a suitable method.

The 90% Confidence Intervals were constructed for the ratios of the means of Ln transformed pharmacokinetic parameters $C_{max,}$ $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for the test and reference formulations.

Measurements were considered bioequivalent if the 90% confidence interval (CI) was fully within the conventionally acceptable range of 80 – 125%. The main pharmacokinetic parameters are summarised in the table below.

Summary of the main pharmacokinetic parameters (N=24)

Statistics			**C_{max} (ng/ml)**	**AUC_{0-t} (hr.ng/ml)**	**AUC_{0-inf} (hr.ng/ml)**	**T_{max} (hr)***
Test Formulation (Mirtazapine 30mg Tablets)	**N**		22	22	22	22
	Mean		64.814	854.542	948.539	1.67
	S.D		18.2428	169.8866	192.3109	0.948
	C.V (%)		28.15	19.88	20.27	51.49
Reference Formulation (Zispin 30 mg Tablets)	**N**		22	22	22	22
	Mean		62.888	960.259	1064.698	2.17
	S.D.		21.9096	267.4927	288.8159	1.250
	C.V (%)		34.84	27.86	27.13	56.28
Difference (T/R%)	**Ln transformed**		105.59	90.95	90.89	-
90% Confidence Interval	**Ln transformed**	**Lower**	95.03	85.03	84.75	-
		Upper	117.31	97.28	97.47	-
		Power (%)	96	100	100	-

* For Tmax instead of mean, median has been used.

The 90% confidence interval of the Test to the Reference formulation of C_{max}, AUC_T and AUC_∞ were all within the conventionally acceptance range of 80-125%. Therefore, the Test formulation is judged to be bioequivalent to the Reference formulation (Zispin 30mg Tablets) on the basis of C_{max} and AUC parameters.

The essentially linear pharmacokinetics of mirtazapine makes it likely that the mirtazapine formulations of lower strength are also bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

Fifty-seven (57) adverse events were reported during the entire duration of the study. Of these, 52 adverse events were "drowsiness" (28 & 24 in Periods I & II respectively), 1 adverse event was "abrasion at base of nail of right middle finger" in Period II while 4 adverse events were "eosinophilia" in post clinical laboratory test results. No serious adverse events were reported.

All subjects complained of sleepiness after administration of study drug in both periods. Diagnosis was drowsiness due to study drug. This adverse event was assessed to be mild in nature, non-serious, expected and having a definite relationship to the study drug. Treatment was not required and the adverse event was resolved completely for all the subjects on the evening of the same day of drug administration in both periods.

EFFICACY

No new data are provided. However, the applicant has provided a critical expert review of 75 publications which demonstrate the effectiveness and safety of mirtazapine.

SAFETY

No new data are submitted. The applicant has provided a review of the clinical safety of mirtazapine. Overall, the incidence of adverse effects compares favourably with that of other

related antidepressants such as amitriptyline. The most common adverse events of mirtazapine are sedation, weight gain and increased appetite.

EXPERT REPORT

A satisfactory Clinical Expert Overview has been submitted with an accompanying CV.

SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET
LABELLING

Satisfactory.

DISCUSSION

Tricyclics and related antidepressants, including mirtazapine, have been available in the EU and the UK for over 10 years. Their use is well established with recognised efficacy and acceptable safety.

CONCLUSIONS

Marketing authorisations may be granted on medical grounds.

STATISTICAL ASSESSMENT

The applicant supplied a single bioequivalence study to support this application. This was a randomised, open-label, two-way crossover trial in 28 fasted healthy volunteers.

The study compared the applicant's generic Mirtazapine 30mg Tablets (test) with the originator product Zispin (Mirtazapine) 30mg Tablets (reference).

Volunteers received both treatments in a randomised order, receiving a single dose in each of two study periods, the periods being separated by a washout period of 14 days. Blood samples were taken pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 24, 36, 48 and 72 hours after dosing.

Patient accountability

There were 28 subjects randomised into the trial, of which 24 completed both study periods as scheduled. Subject 9 was withdrawn from the study in Period II as he was "found to be in a drunken state" when reporting for that period. There were three subjects, 14, 19 and 26, who were withdrawn from period II as they did not report to the clinic for Period II.

The aim of the trial was to have 24 patients who completed both periods. Subjects 1-24 were to be included in the analysis. Subjects 25-28 were "replacements" only to be included in the analysis if any of patients 1-24 did not complete the trial. This is not the appropriate approach. The data from all patients who complete both periods should be included in the analysis.

In the event subjects 9, 14 and 19 did not complete the trial. All three were from the same sequence, having taken the reference product in the first period. The applicant looked to replace them with patients who also took the reference product in the first period, in order to

maintain a balanced design with the same number of patients on each sequence. Subjects 26 and 27 were the relevant replacement patients, but subject 26 had also withdrawn after Period 1. Hence only subject 27 was included in the analysis as a replacement leaving 2 of the missing subjects "un-replaced". Subjects 25 and 28 were excluded from the analysis as they were in the sequence which did not require replacements.

This strategy is not appropriate. The applicant should have included all of the replacement patients in the analysis. It is not a problem to have an unbalanced design, as the statistical analysis can easily account for this. In fact the applicant's approach has already yielded an unbalanced design, with 12 patients on one sequence and only 10 on the other because of the shortage of replacement subjects who took the reference product in Period I.

Results

The percentage of $AUC_{0-\infty}$ which was extrapolated was less then 20% for all patients, indicating that the sampling schedule was sufficient to characterise the concentration curves.

The results when only 22 subjects were included are shown in the table below.

	Geometric mean (ng/ml)		Ratio: Test/Reference	
Parameter	Test	Reference	Point estimate	90% CI
AUC_{0-t}	837.80	927.29	0.91	0.85-0.97
$AUC_{0-\infty}$	929.33	1030.12	0.91	0.85-0.97
C_{max}	62.46	59.53	1.06	0.95-1.17

Analysis from ANOVA on log-transformed data with terms for sequence, subject within sequence, period and treatment.

The statistical assessor repeated the calculations including all 24 subjects who completed the trial. The confidence intervals did not change greatly with the inclusion of the additional 2 subjects.

	Geometric mean (ng/ml)		Ratio: Test/Reference	
Parameter	Test	Reference	Point estimate	90% CI
AUC_{0-t}	850.23	928.78	0.92	0.87-0.99
$AUC_{0-\infty}$	939.85	1031.54	0.92	0.86-0.99
C_{max}	63.18	59.45	1.06	0.96-1.18

Statistical assessor's calculations

There is some evidence that the AUC is lower for the test product than the reference product, however the confidence intervals are contained within 0.80-1.25 so any difference is of a magnitude that is not considered to be of clinical relevance.

Conclusion

The 90% confidence intervals for all 3 parameters are contained within 0.80-1.25, irrespective of whether we look at the 24 or 22 patients analysis. This provides good evidence that in the fasted state the test 30mg tablets are bioequivalent to the originator product.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Mirtazapine 15mg, 30mg and 45mg 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

While the applicant has not submitted any preclinical data, it does not appear that there any particular concerns with this drug. There is considerable clinical experience with mirtazapine and this would, in any case, override preclinical concerns.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Mirtazapine 30mg Tablets and Zispin (Mirtazapine) 30mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Zispin (Mirtazapine) Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with the active ingredient mirtazapine is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

MIRTAZAPINE 30MG TABLETS
PL 20532/0019

MIRTAZAPINE 45MG TABLETS
PL 20532/0020

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Mirtazapine Tablets on 30 March 2004.
2	The MHRA's assessment of the submitted clinical data was completed on 26 January 2005.
3	The MHRA's preclinical assessment was completed on 20 February 2005.
4	Further information (clinical) was requested from the company on 6 April 2005.
5	The MHRA's assessment of the submitted quality data was completed on 2 June 2005.
6	The applicant's response to further information (quality) request was received on 4 July 2005.
7	The MHRA completed its assessment of the applications on 27 July 2006.
8	The applications were determined on 31 July 2006.

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

MIRTAZAPINE 30MG TABLETS
PL 20532/0019

MIRTAZAPINE 45MG TABLETS
PL 20532/0020

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mirtazapine 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Mirtazapine 15 mg.

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablet (tablet)

Mirtazapine 15 mg tablets are yellow, biconvex, capsule shaped, film-coated tablets with a score line in between 0 and 8 debossed on one side and 'A' on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of depressive illness.

4.2. Posology and method of administration

Mirtazapine tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Adults
Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly
The recommended dose is the same as that for adults. In elderly patients, an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children
Since safety and efficacy of Mirtazapine has not been established in children, it is not recommended to treat children with Mirtazapine tablets.

Renal and hepatic insufficiency
The clearance of Mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine tablets to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Mirtazapine tablets are suitable for once-a-day administration preferably as a single night-time dose before going to bed. Mirtazapine tablets may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Withdrawal symptoms seen on discontinuation of Mirtazapine

Abrupt discontinuation should be avoided (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Hypersensitivity to Mirtazapine or any of the other ingredients of Mirtazapine tablets.

4.4. Special warnings and precautions for use

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported as a rare occurrence with Mirtazapine. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment. With respect to agranulocytosis, the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome. As with other antidepressants, Mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where

there is an increase in seizure frequency. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored. From clinical experience it appears that insults occur rarely in patients treated with Mirtazapine.

- hepatic or renal insufficiency.

- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered.

- low blood pressure.

- diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

As with other antidepressants, care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Mirtazapine possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Mirtazapine because of its very weak anticholinergic activity)

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.

- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase.

- as improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of suicide is inherent in depression, and may persist until significant remission occurs. It is general clinical experience with all therapies for depression, that the risk of suicide may increase in the early stages of recovery.

- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise.

- elderly patients are often more sensitive, especially with regard to the side- effects of antidepressants. During clinical research with Mirtazapine, side- effects have not been reported more often in elderly patients than in other age groups; however experience until now is limited.

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

Suicide / suicidal thoughts

- Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide – related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.
- Other psychiatric conditions for which mirtazapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.
- Patients with a history of suicide – related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
- Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.
- Use in children and adolescents under 18 years of age
- Mirtazapine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide - related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Psychomotor restlessness

The use of mirtazapine has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of mirtazapine.

Withdrawal symptoms seen on discontinuation of mirtazapine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials,

adverse events seen on treatment discontinuation occurred in approximately 15% of patients treated with mirtazapine. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, agitation, anxiety, headache and nausea and / or vomiting are the most commonly reported reactions. Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 – 3 months or more). It is therefore advised that mirtazapine should be gradually tapered when discontinuing treatment over a period of several weeks, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Mirtazapine", Section 4.2 Posology and Method of Administration).

4.5. Interactions with other medicinal products and other forms of interaction

- Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine tablets.

- Mirtazapine tablets should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.

- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Mirtazapine tablets.

- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A.

- Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, erythromycin and nefazodone are co-administered with mirtazapine.

- Co-administration of the potent inhibitor of CYP3A4, ketoconazole increased the peak plasma levels and AUC by approximately 30 and 45% respectively.

- Carbamazepine, an inducer of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45-60%. Phenytoin increased the clearance of mirtazapine in a similar fashion. When carbamazepine or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, mirtazapine dosing may have to be decreased.

- Bioavailability of mirtazapine increased by more than 50% when co- administered with cimetidine. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended.

- Mirtazapine caused a small but clinically insignificant increase in INR in subjects treated with warfarin.

Absence of interactions

- In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

- No relevant clinical effects or changes in pharmacokinetics have been observed in man with concurrent administration of mirtazapine and lithium.

- A number of clinical interaction studies, and a study of mirtazapine treatment following SSRI treatment failure have been performed with mirtazapine and SSRIs. Until now, no clinical interactions, pharmacodynamic or pharmacokinetic, have been encountered.

4.6. Pregnancy and lactation

There are no adequate data from the use of mirtazapine in pregnant women. Studies in animals have not shown any teratogenic effect or reproductive toxicity of clinical relevance (see 5.3 Preclinical safety data). The potential risk for human is unknown. Mirtazapine should not be used during pregnancy unless clearly indicated following a careful clinical risk/benefit consideration.

Women of child – bearing potential should employ an adequate method of contraception if taking mirtazapine.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of mirtazapine in breast-feeding mothers is not recommended. No human data are available.

4.7. Effects on ability to drive and use machines

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may impair alertness and concentration. Patients treated with Mirtazapine tablets should therefore be cautioned about their ability to drive a car or operate hazardous machinery.

4.8. Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine. The following adverse effects have been reported:

Very common	: affecting more than 1 in 10 patients treated
Common	: affecting fewer than 10 in 100 patients treated
Uncommon	: affecting fewer than 10 in 1000 patients treated
Rare	: affecting fewer than 10 in 10,000 patients treated

Blood and the lymphatic system disorders

Rare (>1/10,000)
Reversible agranulocytosis has been reported as a rare occurrence with Mirtazapine. (see also section 4.4 'Special warnings and special precautions for use')

Metabolism and nutrition disorders

Common (>1/100)
Increase in appetite and weight gain

Psychiatric disorders

Rare (>1/10,000)

Nightmares/vivid dreams, psychomotor restlessness including akathisia (see section 4.4 Special warnings and special precautions for use).

Nervous system disorders

Uncommon (>1/1000)

Dizziness, Headache

Rare (>1/10,000)
Mania, convulsions (insults), tremor, myoclonus. There have been rare reports of agitation and hallucinations, although these symptoms may be related to underlying disease. (These effects have also been reported under placebo treatment in placebo-controlled studies with Mirtazapine), Paraesthesia.

Cardiac disorders

Rare (>1/10,000)
(Orthostatic) hypotension.

Hepato-biliary disorders

Uncommon(>1/1000)
Increases in liver enzyme levels.

Skin and subcutaneous tissue disorders

Rare (>1/10,000)
Rash

Musculoskeletal, connective tissue and bone disorders

Rare (>1/10,000)
Restless legs, Arthralgia/myalgia

General disorders

Common (>1/100)

Generalised or local oedema. Drowsiness/sedation/ fatigue, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy).

Withdrawal symptoms seen on discontinuation of mirtazapine treatment

Discontinuation of mirtazapine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, agitation, anxiety, headache and nausea and / or vomiting are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and / or prolonged. It is therefore advised that when mirtazapine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

4.9. Overdose

Reports of overdose with Mirtazapine alone indicate that the symptoms are usually mild.

Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension.

Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5. PHARMACOLOGICAL PROPERTIES

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment with Mirtazapine tablets.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-depressant

ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

Dose response

No formal clinical trials were conducted investigating the dose response of mirtazapine. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

5.2. Pharmacokinetic properties

After oral administration of Mirtazapine tablets, the active constituent mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

In rat and rabbit reproductive toxicity studies high doses of mirtazapine (20 and 17 times the maximum human dose on a mg/m^2 basis, respectively) were not associated with teratogenic effects. However, increases in post implantation loss, decreases in pup birth weights, and reductions in pup survival during the first three days of lactation were seen.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mirtazapine 15 mg tablets contain

Core:
Lactose monohydrate, Maize starch, Low substituted Hydroxypropyl Cellulose, Magnesium Stearate (E470b) and Silica Colloidal anhydrous.

Film Coating:
Hypromellose (E464), Titanium dioxide (E 171) and Yellow iron oxide (E 172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Blister packs comprising of 250 µ PVC coated with 60 gsm PVdC & 25 µ aluminium foil.

10/14/28/30/40/50/56/60/70/84/90/100/200/250/500 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road, South Ruislip
HA4 6QD, United Kingdom.
Tel: +44 20 8845 8811.
Fax: +44 20 8845 8795.

8. MARKETING AUTHORISATION NUMBER

PL 20532/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/07/2006

10 DATE OF REVISION OF THE TEXT

31/07/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mirtazapine 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Mirtazapine 30 mg.

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablet (tablet)

Mirtazapine 30 mg tablets are Reddish Brown, biconvex, capsule shaped, film coated tablets with a score line in between 0 and 9 debossed on one side and 'A' on the other side

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of depressive illness.

4.2. Posology and method of administration

Mirtazapine tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Adults
Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly
The recommended dose is the same as that for adults. In elderly patients, an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children
Since safety and efficacy of Mirtazapine has not been established in children, it is not recommended to treat children with Mirtazapine tablets.

Renal and hepatic insufficiency
The clearance of Mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine tablets to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Mirtazapine tablets are suitable for once-a-day administration preferably as a single night-time dose before going to bed. Mirtazapine tablets may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Withdrawal symptoms seen on discontinuation of Mirtazapine

Abrupt discontinuation should be avoided (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Hypersensitivity to Mirtazapine or any of the other ingredients of Mirtazapine tablets.

4.4. Special warnings and precautions for use

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported as a rare occurrence with Mirtazapine. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment. With respect to agranulocytosis, the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome. As with other antidepressants, Mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled

epilepsy should be carefully monitored. From clinical experience it appears that insults occur rarely in patients treated with Mirtazapine

- hepatic or renal insufficiency.

- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered.

- low blood pressure.

- diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

As with other antidepressants, care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Mirtazapine possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Mirtazapine because of its very weak anticholinergic activity)

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.

- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase.

- as improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of suicide is inherent in depression, and may persist until significant remission occurs. It is general clinical experience with all therapies for depression, that the risk of suicide may increase in the early stages of recovery.

- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise.

- elderly patients are often more sensitive, especially with regard to the side- effects of antidepressants. During clinical research with Mirtazapine, side- effects have not been reported more often in elderly patients than in other age groups; however experience until now is limited.

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

Suicide / suicidal thoughts

- Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide – related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.
- Other psychiatric conditions for which mirtazapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.
- Patients with a history of suicide – related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
- Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.
- Use in children and adolescents under 18 years of age
- Mirtazapine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide - related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Psychomotor restlessness

The use of mirtazapine has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of mirtazapine.

Withdrawal symptoms seen on discontinuation of mirtazapine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials,

adverse events seen on treatment discontinuation occurred in approximately 15% of patients treated with mirtazapine. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, agitation, anxiety, headache and nausea and / or vomiting are the most commonly reported reactions. Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 – 3 months or more). It is therefore advised that mirtazapine should be gradually tapered when discontinuing treatment over a period of several weeks, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Mirtazapine", Section 4.2 Posology and Method of Administration).

4.5. Interactions with other medicinal products and other forms of interaction

- Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine tablets.

- Mirtazapine tablets should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.

- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Mirtazapine tablets.

- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A.

- Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, erythromycin and nefazodone are co-administered with mirtazapine.

- Co-administration of the potent inhibitor of CYP3A4, ketoconazole increased the peak plasma levels and AUC by approximately 30 and 45% respectively.

- Carbamazepine, an inducer of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45-60%. Phenytoin increased the clearance of mirtazapine in a similar fashion. When carbamazepine or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, mirtazapine dosing may have to be decreased.

- Bioavailability of mirtazapine increased by more than 50% when co- administered with cimetidine. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended.

- Mirtazapine caused a small but clinically insignificant increase in INR in subjects treated with warfarin.

Absence of interactions

- In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

- No relevant clinical effects or changes in pharmacokinetics have been observed in man with concurrent administration of mirtazapine and lithium.

- A number of clinical interaction studies, and a study of mirtazapine treatment following SSRI treatment failure have been performed with mirtazapine and SSRIs. Until now, no clinical interactions, pharmacodynamic or pharmacokinetic, have been encountered.

4.6. Pregnancy and lactation

There are no adequate data from the use of mirtazapine in pregnant women. Studies in animals have not shown any teratogenic effect or reproductive toxicity of clinical relevance (see 5.3 Preclinical safety data). The potential risk for human is unknown. Mirtazapine should not be used during pregnancy unless clearly indicated following a careful clinical risk/benefit consideration.

Women of child – bearing potential should employ an adequate method of contraception if taking mirtazapine.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of mirtazapine in breast-feeding mothers is not recommended. No human data are available.

4.7. Effects on ability to drive and use machines

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may impair alertness and concentration. Patients treated with Mirtazapine tablets should therefore be cautioned about their ability to drive a car or operate hazardous machinery.

4.8. Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine. The following adverse effects have been reported:

Very common : affecting more than 1 in 10 patients treated
Common : affecting fewer than 10 in 100 patients treated
Uncommon : affecting fewer than 10 in 1000 patients treated
Rare : affecting fewer than 10 in 10,000 patients treated

Blood and the lymphatic system disorders

Rare (>1/10,000)

Reversible agranulocytosis has been reported as a rare occurrence with Mirtazapine. (see also section 4.4 'Special warnings and special precautions for use')

Metabolism and nutrition disorders

Common (>1/100)

Increase in appetite and weight gain

Psychiatric disorders

Rare (>1/10,000)

Nightmares/vivid dreams, psychomotor restlessness including akathisia (see section 4.4 Special warnings and special precautions for use).

Nervous system disorders

Uncommon(>1/1000)

Dizziness, Headache

Rare (>1/10,000)

Mania, convulsions (insults), tremor, myoclonus. There have been rare reports of agitation and hallucinations, although these symptoms may be related to underlying disease. (These effects have also been reported under placebo treatment in placebo-controlled studies with mirtazapine), Paraesthesia.

Cardiac disorders

Rare (>1/10,000)

(Orthostatic) hypotension.

Hepato-biliary disorders

Uncommon (>1/1000)

Increases in liver enzyme levels.

Skin and subcutaneous tissue disorders

Rare (>1/10,000)

Rash

Musculoskeletal, connective tissue and bone disorders

Rare (>1/10,000)

Restless legs, Arthralgia/myalgia

General disorders

Common (>1/100)

Generalised or local oedema. Drowsiness/sedation/ fatigue, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy) Although mirtazapine does not cause dependence, abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms which are mild and self-limiting.

Withdrawal symptoms seen on discontinuation of mirtazapine treatment

Discontinuation of mirtazapine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, agitation, anxiety, headache and nausea and / or vomiting are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and / or prolonged. It is therefore advised that when mirtazapine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

4.9. Overdose

Reports of overdose with Mirtazapine alone indicate that the symptoms are usually mild.

Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension.

Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5. PHARMACOLOGICAL PROPERTIES

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and

changes in mood (better in the evening than in the morning). Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment with Mirtazapine tablets.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-depressant

ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

Dose response

No formal clinical trials were conducted investigating the dose response of mirtazapine. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

5.2. Pharmacokinetic properties

After oral administration of Mirtazapine tablets, the active constituent mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers.

Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

In rat and rabbit reproductive toxicity studies high doses of mirtazapine (20 and 17 times the maximum human dose on a mg/m^2 basis, respectively) were not associated with teratogenic effects. However, increases in post implantation loss, decreases in pup birth weights, and reductions in pup survival during the first three days of lactation were seen.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mirtazapine 30 mg tablets contain

Core:
Lactose monohydrate, Maize starch, Low substituted Hydroxypropyl Cellulose, Magnesium Stearate (E470b) and Silica Colloidal anhydrous

Film Coating:
Hypromellose (E464), Titanium dioxide (E 171) Yellow Iron oxide (E172), Red Iron oxide (E172) and Black Iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Blister packs comprising of 250 µ PVC coated with 60 gsm PVdC & 25 µ aluminium foil.

10/14/28/30/40/50/56/60/70/84/90/100/200/250/500 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road, South Ruislip
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Fax: +44 20 8845 8795.

8. MARKETING AUTHORISATION NUMBER

PL 20532/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/07/2006

10 DATE OF REVISION OF THE TEXT

31/07/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mirtazapine 45 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Mirtazapine 45 mg.

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablet (tablet)

Mirtazapine 45 mg tablets are White, biconvex, capsule shaped film coated tablets with '10' debossed on one side and 'A' on the other side

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of depressive illness.

4.2. Posology and method of administration

Mirtazapine tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Adults
Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly
The recommended dose is the same as that for adults. In elderly patients, an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children
Since safety and efficacy of Mirtazapine has not been established in children, it is not recommended to treat children with Mirtazapine tablets.

Renal and hepatic insufficiency
The clearance of Mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine tablets to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Mirtazapine tablets are suitable for once-a-day administration preferably as a single night-time dose before going to bed. Mirtazapine tablets may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Withdrawal symptoms seen on discontinuation of Mirtazapine

Abrupt discontinuation should be avoided (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Hypersensitivity to Mirtazapine or any of the other ingredients of Mirtazapine tablets.

4.4. Special warnings and precautions for use

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported as a rare occurrence with Mirtazapine. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment. With respect to agranulocytosis, the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome. As with other antidepressants, Mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored. From clinical experience it appears that insults occur rarely in patients treated with Mirtazapine

- hepatic or renal insufficiency

- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered.

- low blood pressure.

- diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

As with other antidepressants, care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Mirtazapine possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Mirtazapine because of its very weak anticholinergic activity)

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.

- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase.

- as improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of suicide is inherent in depression, and may persist until significant remission occurs. It is general clinical experience with all therapies for depression, that the risk of suicide may increase in the early stages of recovery.

- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise.

- elderly patients are often more sensitive, especially with regard to the side-effects of antidepressants. During clinical research with Mirtazapine, side- effects have not been reported more often in elderly patients than in other age groups; however experience until now is limited.

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

Suicide / suicidal thoughts

- Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide – related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.
- Other psychiatric conditions for which mirtazapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.
- Patients with a history of suicide – related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
- Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.
- Use in children and adolescents under 18 years of age
- Mirtazapine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide - related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Psychomotor restlessness

The use of mirtazapine has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of mirtazapine.

Withdrawal symptoms seen on discontinuation of mirtazapine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials, adverse events seen on treatment discontinuation occurred in approximately 15% of patients treated with mirtazapine. The risk of withdrawal symptoms may be

dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, agitation, anxiety, headache and nausea and / or vomiting are the most commonly reported reactions. Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 – 3 months or more). It is therefore advised that mirtazapine should be gradually tapered when discontinuing treatment over a period of several weeks, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Mirtazapine", Section 4.2 Posology and Method of Administration).

4.5. Interactions with other medicinal products and other forms of interaction

- Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine tablets.

- Mirtazapine tablets should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.

- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Mirtazapine tablets.

- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A.

- Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, erythromycin and nefazodone are co-administered with mirtazapine.

- Co-administration of the potent inhibitor of CYP3A4, ketoconazole increased the peak plasma levels and AUC by approximately 30 and 45% respectively.

- Carbamazepine, an inducer of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45-60%. Phenytoin increased the clearance of mirtazapine in a similar fashion. When carbamazepine or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, mirtazapine dosing may have to be decreased.

- Bioavailability of mirtazapine increased by more than 50% when co- administered with cimetidine. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended.

- Mirtazapine caused a small but clinically insignificant increase in INR in subjects treated with warfarin.

Absence of interactions

- In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

- No relevant clinical effects or changes in pharmacokinetics have been observed in man with concurrent administration of mirtazapine and lithium.

- A number of clinical interaction studies, and a study of mirtazapine treatment following SSRI treatment failure have been performed with mirtazapine and SSRIs. Until now, no clinical interactions, pharmacodynamic or pharmacokinetic, have been encountered.

4.6. Pregnancy and lactation

There are no adequate data from the use of mirtazapine in pregnant women. Studies in animals have not shown any teratogenic effect or reproductive toxicity of clinical relevance (see 5.3 Preclinical safety data). The potential risk for human is unknown. Mirtazapine should not be used during pregnancy unless clearly indicated following a careful clinical risk/benefit consideration.

Women of child – bearing potential should employ an adequate method of contraception if taking mirtazapine.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of mirtazapine in breast-feeding mothers is not recommended. No human data are available.

4.7. Effects on ability to drive and use machines

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may impair alertness and concentration. Patients treated with Mirtazapine tablets should therefore be cautioned about their ability to drive a car or operate hazardous machinery.

4.8. Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine. The following adverse effects have been reported:

Very common : affecting more than 1 in 10 patients treated
Common : affecting fewer than 10 in 100 patients treated

Uncommon : affecting fewer than 10 in 1000 patients treated
Rare : affecting fewer than 10 in 10,000 patients treated

Blood and the lymphatic system disorders

Rare (>1/10,000)
Reversible agranulocytosis has been reported as a rare occurrence with Mirtazapine. (see also section 4.4 'Special warnings and special precautions for use')

Metabolism and nutrition disorders

Common (>1/100)

Increase in appetite and weight gain

Psychiatric disorders

Rare (>1/10,000)

Nightmares/vivid dreams, psychomotor restlessness including akathisia (see section 4.4 Special warnings and special precautions for use).

Nervous system disorders

Uncommon(>1/1000)

Dizziness, Headache

Rare (>1/10,000)

Mania, convulsions (insults), tremor, myoclonus. There have been rare reports of agitation and hallucinations, although these symptoms may be related to underlying disease. *(*These effects have also been reported under placebo treatment in placebo-controlled studies with mirtazapine*),* Paraesthesia.

Cardiac disorders

Rare (>1/10,000)

(Orthostatic) hypotension.

Hepato-biliary disorders

Uncommon(>1/1000)

Increases in liver enzyme levels.

Skin and subcutaneous tissue disorders

Rare (>1/10,000)

Rash

Musculoskeletal, connective tissue and bone disorders

Rare (>1/10,000)

Restless legs, Arthralgia/myalgia

General disorders

Common (>1/100)

Generalised or local oedema. Drowsiness/sedation/ fatigue, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy).

Withdrawal symptoms seen on discontinuation of mirtazapine treatment

Discontinuation of mirtazapine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, agitation, anxiety, headache and nausea and / or vomiting are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and / or prolonged. It is therefore advised that when mirtazapine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

4.9. Overdose

Reports of overdose with Mirtazapine alone indicate that the symptoms are usually mild.

Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension.

Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5. PHARMACOLOGICAL PROPERTIES

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment with Mirtazapine tablets.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-depressant

ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

Dose response

No formal clinical trials were conducted investigating the dose response of mirtazapine. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

5.2. Pharmacokinetic properties

After oral administration of Mirtazapine tablets, the active constituent mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

In rat and rabbit reproductive toxicity studies high doses of mirtazapine (20 and 17 times the maximum human dose on a mg/m^2 basis, respectively) were not associated with teratogenic effects. However, increases in post implantation loss, decreases in pup birth weights, and reductions in pup survival during the first three days of lactation were seen.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mirtazapine 45 mg tablets contain

Core:
Lactose monohydrate, Maize starch, Low substituted Hydroxypropyl Cellulose, Magnesium Stearate (E 470b), Hydroxypropyl cellulose and Silica Colloidal anhydrous

Film Coating:
Hypromellose (E464) and Titanium dioxide (E 171)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Blister packs comprising of 250 µ PVC coated with 60 gsm PVdC & 25 µ aluminium foil.

10/14/28/30/40/50/56/60/70/84/90/100/200/250/500 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
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8. MARKETING AUTHORISATION NUMBER

PL 20532/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

31/07/2006

Patient Information Leaflet

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

MIRTAZAPINE 30MG TABLETS
PL 20532/0019

MIRTAZAPINE 45MG TABLETS
PL 20532/0020

Package Leaflet: Information for the User

Mirtazapine 15, 30 & 45 mg tablets

(Mirtazapine)

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

1) What Mirtazapine tablets are and what are they used for

Mirtazapine tablets contain the active ingredient Mirtazapine and are used to treat depression. Depression is linked to a shortage of substances which carry messages in the brain (including serotonin and noradrenaline). Mirtazapine helps to relieve the shortage of these 'brain messengers'.

If you have been feeling sad, tearful, unable to sleep properly or to enjoy life as you used to, Mirtazapine tablets may help you to feel better. If you are not sure why you are taking these tablets, ask you doctor.

It may take 2 to 4 weeks before you start to feel and sleep better. It is important to take Mirtazapine tablets every day and not to stop taking them unless your doctor tells you to. If you do, your symptoms may come back.

2) Before you take Mirtazapine tablets

Do not take Mirtazapine tablets

- If you are allergic to Mirtazapine or any other ingredients of Mirtazapine tablets.

Take special care with Mirtazapine tablets

If you have or ever had:

- an epileptic fit.
- liver disease (including jaundice) or kidney disease.
- a heart disease such as angina and recent myocardial infarct
- low blood pressure.
- eye disease such as glaucoma.
- difficulty in passing water (urinating), which might be caused by enlarged prostrate
- diabetes.
- psychiatric disorders such as schizophrenia or manic depression.

Use in children and adolescents under 18 years of age

Mirtazapine should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Mirtazapine for patients under 18 because he / she decides that this is in their best interests. If your doctor has prescribed Mirtazapine for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Mirtazapine. Also the long term safety effects concerning both, maturation and cognitive and behavioural development of Mirtazapine in this age group have not yet been demonstrated.

Thoughts of harming yourself

Some people who are depressed think of harming or killing themselves. This may be increased when you first start taking antidepressants, since these medicines all take time to work. You may be more likely to think of harming yourself if you:

- are a young adult, for example aged 18 to 29
- have previously had thoughts about killing or harming yourself.

If any time you start to feel worse, or think of killing yourself, see your doctor or go to a hospital straight away.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken the following medicines or any other medicines including medicines obtained without a prescription.

- Drugs for infection such as erythromycin, nefazodone, rifampicin, azole antifungals, ketoconazole and HIV protease inhibitors.
- Drugs for epilepsy such as carbamazepine and phenytoin.
- Drugs for indigestion or stomach ulcers such as cimetidine.
- Drugs to prevent blood clotting such as warfarin.
- Other drugs for the treatment of depression such as mono amino oxidase (MAO) inhibitors.
- Drugs for anxiety or insomnia such as benzodiazepines.

Taking Mirtazapine tablets with food and drink

You can take Mirtazapine with or without food. Swallow the tablets with water. Your doctor may advise you to take half tablet of 15 or 30 mg. Do not consume alcohol during the treatment with Mirtazapine tablets.

Pregnancy and breast feeding

The possible effects of Mirtazapine tablets on unborn child are unknown.

You must tell your doctor if you are pregnant or if you think you are pregnant. The doctor will decide if Mirtazapine tablets are right for you.

If you are a woman taking Mirtazapine tablets, you need to use reliable contraception (the Pill, a cap, an IUD, implants or condoms).

The effects of Mirtazapine tablets on nursing infants are unknown. You must tell your doctor if you are breast feeding so that the doctor can decide if Mirtazapine tablets are right for you.

Driving and using machines

Antidepressants can affect your concentration or judgement. When you first start taking Mirtazapine tablets, make sure your abilities are not affected before you drive or operate machinery.

Important information about some of the ingredients of Mirtazapine tablets

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3) How to take Mirtazapine tablets

Always take Mirtazapine tablets exactly as your doctor has told you. Your doctor may advise you to take half tablet of 15 or 30 mg. You should check with your doctor or pharmacist if you are unsure.

Swallow the tablets with a drink of water. It is best to take them at the same time each day with or without food. Keep taking your tablets everyday.

The usual starting dose of Mirtazapine tablets for most patients is 15 mg everyday. Your doctor may advise you to increase your dose after a few days to the amount that may be best for you. You may need to take Mirtazapine tablets for up to 2 - 4 weeks before you start to feel better. Your doctor will want to monitor your progress closely during this period.

You must keep taking Mirtazapine tablets to help you get better. It is best to take Mirtazapine tablets as a single dose before you go to bed, as it will probably help you sleep. However, your doctor may suggest you to split your dose - half your daily dose in the morning and the other half before you go to bed. Only take Mirtazapine tablets as your doctor or pharmacist tells you to.

Use in children and adolescents under 18 years of age

Since safety and efficacy of Mirtazapine have not been established in children it is not recommended to treat children with Mirtazapine tablets. (See section "Take special care with Mirtazapine tablets".)

If you take more Mirtazapine tablets than you should

Too many tablets at once can be dangerous. If you take too many tablets tell your doctor. If you are unable to contact your doctor, go to your local hospital casualty department at once.

The most likely signs of overdose are drowsiness and disorientation.

If you forget to take Mirtazapine tablets

If you forget to take your medicine, do not worry and take the next dose at the right time. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Mirtazapine tablets

Do not stop taking Mirtazapine tablets unless your doctor tells you to even if you feel better. Your doctor will advise you when to discontinue the treatment. Symptoms such as anxiety, headache, sick-feeling may occur if you stop taking Mirtazapine tablets suddenly. It is even possible that some of your symptoms may come back. Once you are feeling better, talk to your doctor, who will tell you how to reduce the dose gradually.

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

4) Possible side effects

Like all medicines, Mirtazapine tablets can cause side effects, although not everybody gets them. The frequency of the side effects can be classified as follows :

Very common : affecting more than 1 in 10 patients treated
Common : affecting fewer than 10 in 100 patients treated
Uncommon : affecting fewer than 10 in 1000 patient treated
Rare : affecting fewer than 10 in 10,000 patient treated

Blood and lymphatic system disorders

Rare: Mirtazapine can cause temporary fall in the number of white blood cells in the blood. Hence the resistance to infections may reduce during the first few weeks of the treatment with this medicine. The signs of infection may be fever, sore throat, mouth ulcer or stomach upset. Please contact your doctor if any of these symptoms occur to you.

Metabolism and nutrition disorders

Common: Increase in appetite and weight gain.

Psychiatric disorders

Rare: Nightmares, vivid dreams, restlessness (inability to sit still).

Nervous system disorders

Uncommon: Feeling dizzy, headache.

Rare: Fits (seizures and convulsions), mania (feeling elated or emotionally "high"), hallucinations, feeling agitated, shakiness or tremor, feeling of numbness or "pins and needles" in the body.

Cardiac disorders

Rare: Faint especially when standing up suddenly due to fall in blood pressure.

Hepatobiliary disorders

Uncommon: Yellowing of skin or eyes.

Skin and subcutaneous tissue disorders

Rare: Rash or skin eruptions.

Musculoskeletal and connective tissue disorders

Rare: Restless legs, pains in joints and muscles, muscle twitching.

General disorders

Common: Swelling of lips, face, tongue and ankles caused by fluid retention (oedema), drowsiness/feeling faint (sedation)/fatigue during first few weeks of the treatment.

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.

5) How to store Mirtazapine tablets

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Store in the original package.

Do not use Mirtazapine tablets after the expiry date, which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.These measures will help to protect the environment.

6) Further information

What Mirtazapine tablets contain

- The active ingredient is Mirtazapine. Each film coated tablet containg 15, 30 or 45 mg Mirtazapine.
- The other ingredients are lactose monohydrate, maize starch, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, magnesium stearate (E470b), silica colloidal anhydrous, hypromellose (E464) and titanium dioxide (E 171).

The 15 mg tablets also contain yellow iron oxide (E 172).
The 30 mg tablets also contain yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172).

What Mirtazapine tablets look like and contents of the pack

Mirtazapine 15 mg tablets are yellow, biconvex, capsule shaped film coated tablets with a score line in between '0' and '8' debossed on one side and 'A' on other side.

Mirtazapine 30 mg tablets are reddish brown, biconvex, capsule shaped film coated tablets with a score line in between '0' and '9' debossed on one side and 'A' other side.

Mirtazapine 45 mg tablets are white, biconvex, capsule shaped film coated tablets debossed with '10' on one side and 'A' on the other side.

Mirtazapine 15, 30 and 45 mg tablets are available in PVC coated PVdC blister packs of 10/14/28/30/40/50/56/60/70/84/90/100/200/250/500 tablets. Not all packs may be marketed.

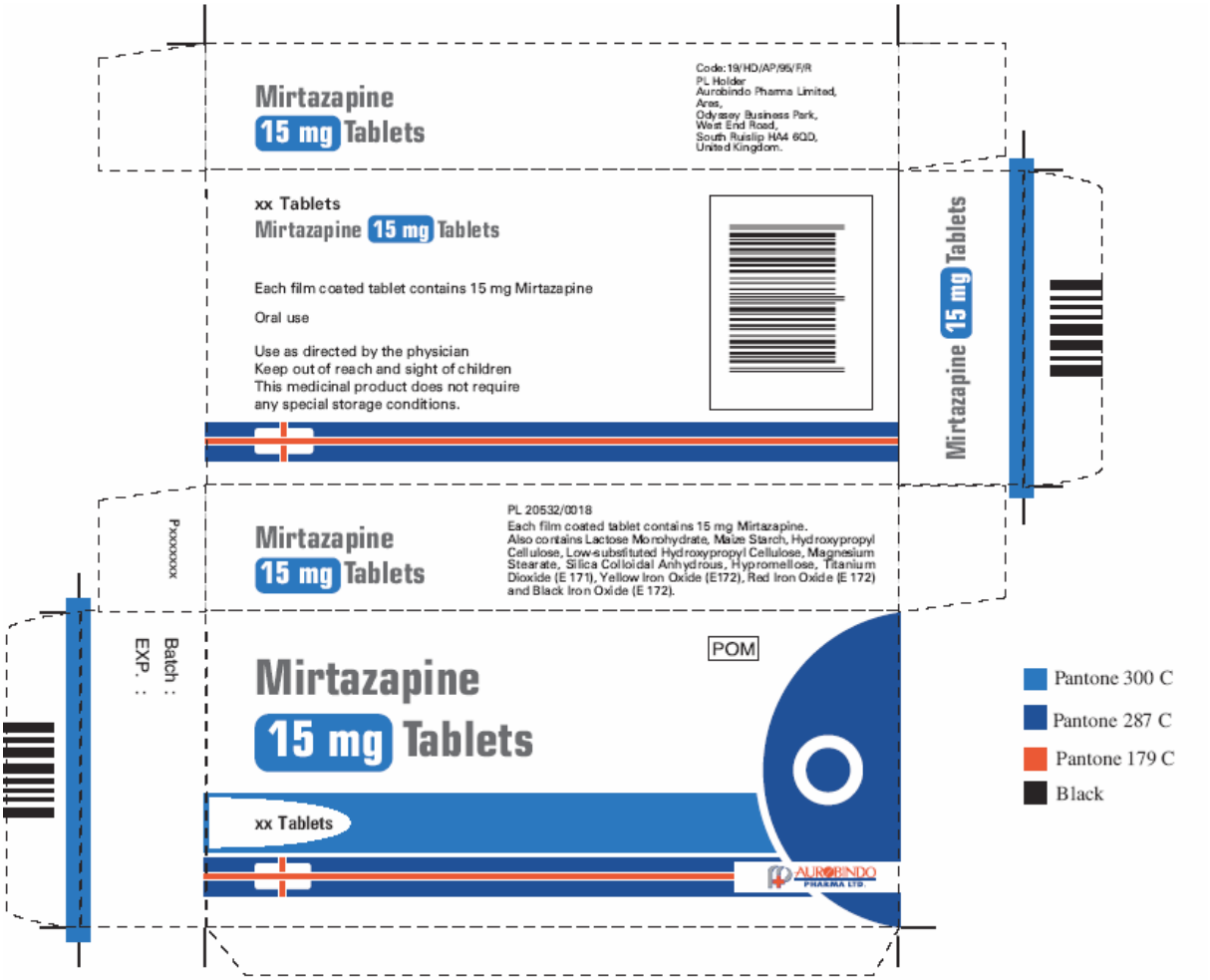
Marketing Authorisation Holder	Manufacturer
Aurobindo Pharma Limited, Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD, United Kingdom. Tel : ++ 44 20 8845 8811 Fax : ++ 44 20 8845 8795	Aurex Generics Limited, Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD, United Kingdom. Tel : ++ 44 20 8845 8811 Fax : ++ 44 20 8845 8795

This leaflet was last approved in MM / YYYY.

Pxxxxxxx

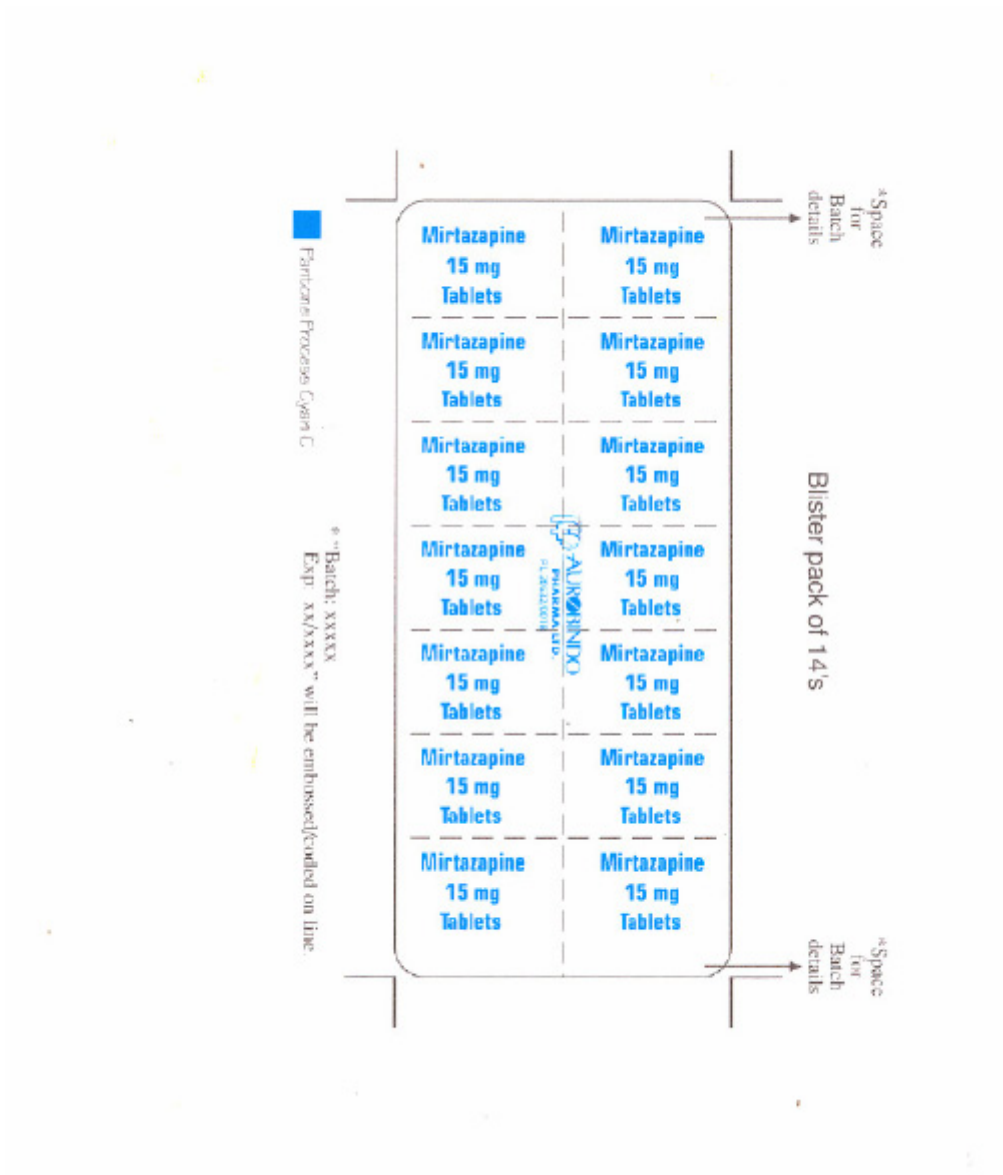
Labels/Packaging

MIRTAZAPINE 15MG TABLETS
PL 20532/0018

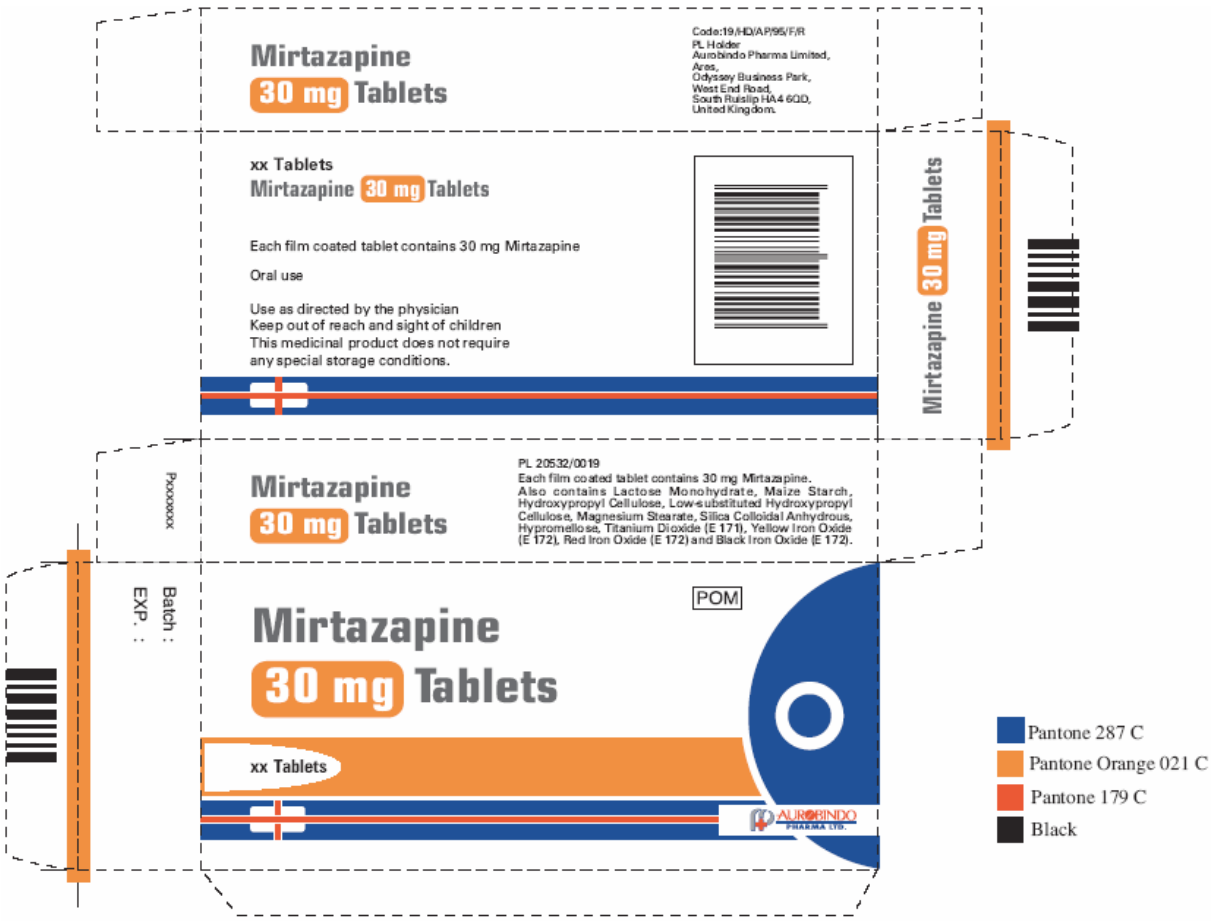


xx marketed pack size will be mentioned in the actual printed carton.
Note : Carton size is subject to change depending on pack sizes

MIRTAZAPINE 15MG TABLETS
PL 20532/0018



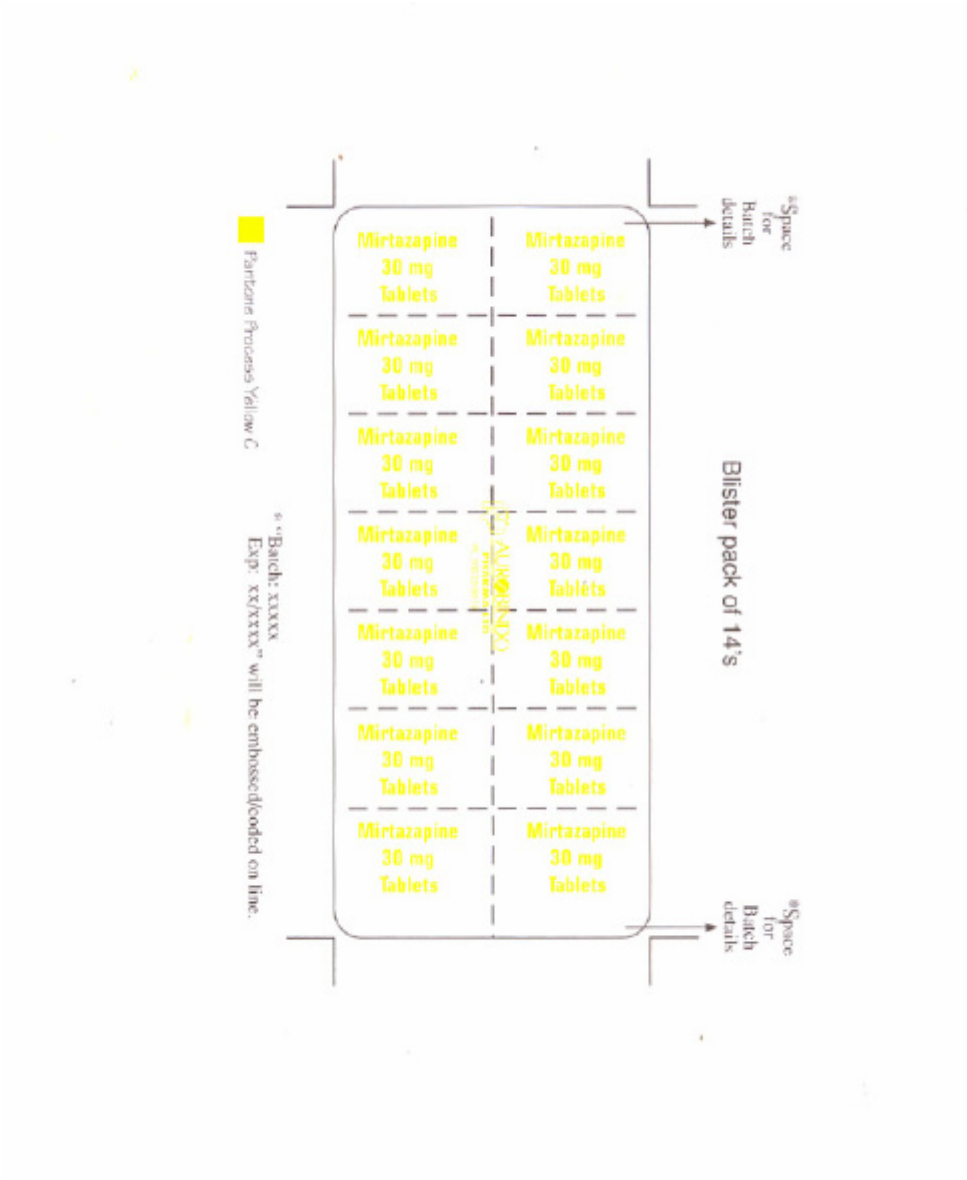
MIRTAZAPINE 30MG TABLETS
PL 20532/0019



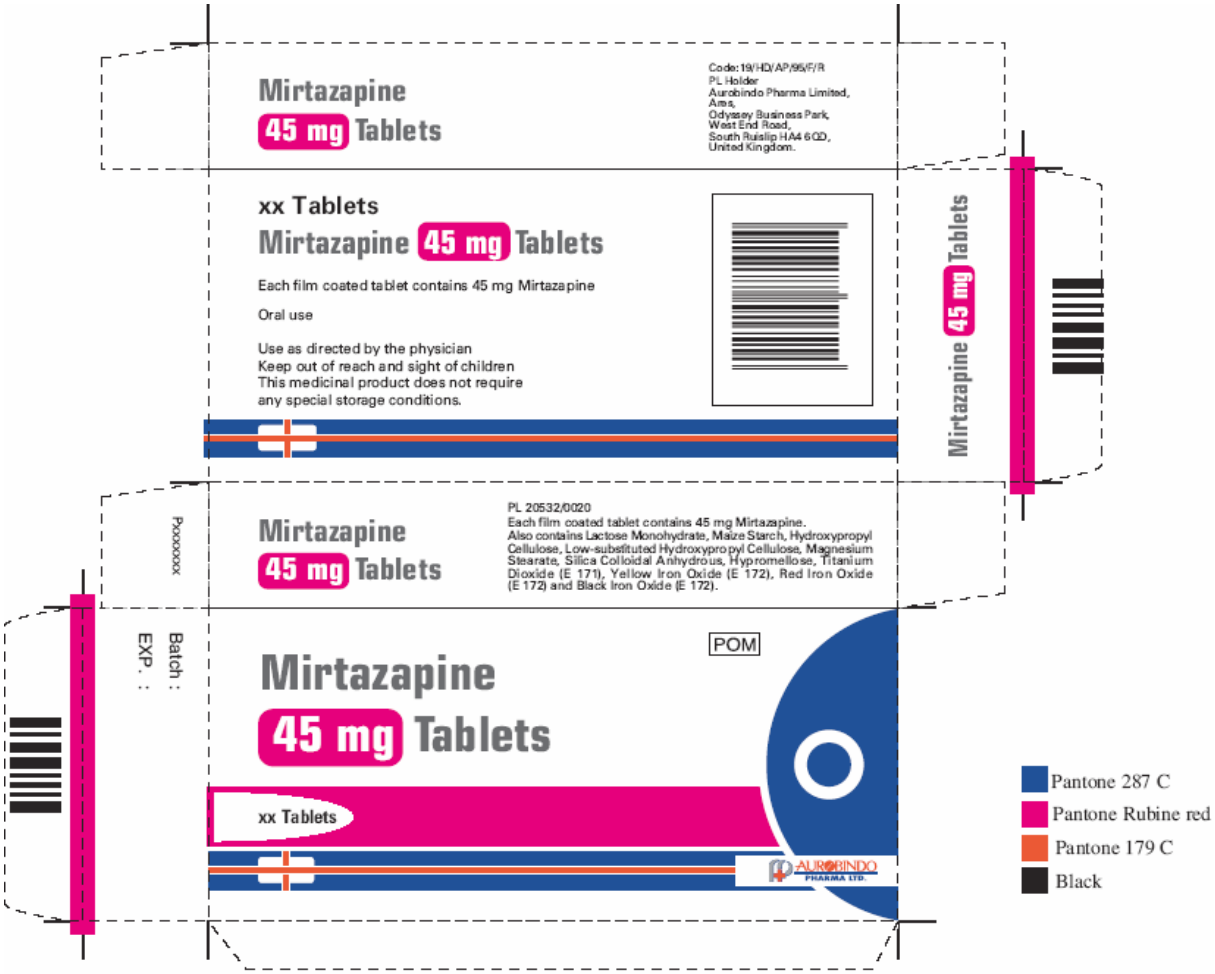
xxmarketed pack size will be mentioned in the actual printed carton.

Note : Carton size is subject to change depending on pack sizes

MIRTAZAPINE 30MG TABLETS
PL 20532/0019



MIRTAZAPINE 45MG TABLETS
PL 20532/0020



xx marketed pack size will be mentioned in the actual printed carton.
Note : Carton size is subject to change depending on pack sizes

MIRTAZAPINE 45MG TABLETS
PL 20532/0020