Public Assessment Report

Mirtazapine 30mg Tablets

PL 04543/0502

Wockhardt UK

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Lay Summary

The MHRA granted a National Marketing Authorisation (licence) to Wockhardt UK for the medicinal product Mirtazapine 30mg Tablets (PL 04543/0502) on 3rd August 2006. Mirtazapine is an antidepressant and is indicated in the treatment of depression.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Mirtazapine 30mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

The Market Authorisation was cancelled on 21st April 2007 at the request of the Market Authorisation Holder.

Scientific Discussion

Introduction

This Public Assessment report is based on the Assessment Report for a National application for Marketing Authorisation for Mirtapazine 30mg Tablets (PL 04543/0502). The National Licence was granted on 3rd August 2006 to Wockhardt UK. The successful application claimed essentially similarity under article 10.1 of directive 2001/83/EC, citing Zispin (Mirtazapine) 30mg tablets (Organon Laboratories Ltd – PL 00065/0145) as the UK reference product.

Mirtazapine is an anti-depressant and is indicated in the treatment of depression. The legal status of Mirtazapine is Prescription Only. No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Mirtapazine 30mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

The Market Authorisation was cancelled on 21st April 2007 at the request of the Market Authorisation Holder.

PHARMACEUTICAL ASSESSMENT

Drug Substance

General Information

Mirtazapine is a white to creamy white crystalline powder that is freely soluble in methanol and in dichloromethane and has a melting point 114to 117°C. It specific optical rotation is -0.5º to +0.5 º.

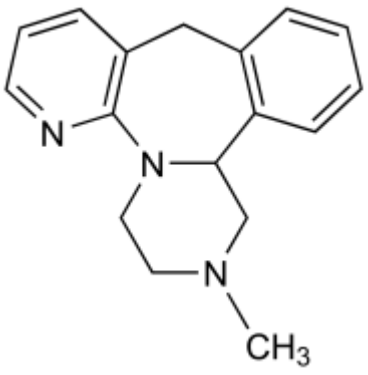
Nomenclature

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



Satisfactory descriptions of the manufacturing process are provided.

Relevant specifications, in-process controls and test methods have been provided for the starting materials including certificates of analysis from the active substance manufacturer. Specifications and certificates of analysis have been supplied for the other materials used in the manufacturing process. Confirmation that the materials used comply with the BSE/TSE requirements has been provided. Reasonable details have been provided for the in-process control of mirtazapine.

Adequate evidence of structure has been provided Satisfactory specifications were provided for the control of the active substance and analytical methods validated. Satisfactory limits for the control of related substances and impurities have been provided.

Conclusion

The manufacturer is an acceptable source of the active ingredient.

Drug Product

The qualitative composition of Mirtazapine 30mg Tablets is shown in below.

Active:

Mirtazapine

Core:

Lactose monohydrate
Hydroxypropylcellulose
Maize starch
Colloidal anhydrous silica
Low-substituted hydroxypropyl cellulose
Magnesium stearate
Purified water

Film-coating:

Opadry Brown 20A56788
(Hydroxypropyl cellulose)
(Hypromellose)
(Titanium dioxide, E171)
(Iron oxide yellow, E172)
(Iron oxide red)
(Iron oxide black)
Purified water

The manufacturer of the finished product has been inspected by MHRA and a letter was provided stating that the site may be named on UK licences. A satisfactory description of the method of manufacture and in process controls was provided.

A signed declaration is provided by the manufacturer of the finished product declaring that the only material of animal origin is lactose monohydrate which is derived from healthy animals.

A satisfactory finished product specification was provided and was supported by certificates of analysis. This was supported by satisfactory batch data, in-process controls and validation of analytical methods. Excipients are controlled by pharmacopoeial methods and so validation was considered unnecessary. Essential similarity in terms of active, impurities and dissolution was demonstrated. Stablity data showed little change over 24 months and a shelf life of 24 months was agreed.

PRE-CLINICAL ASSESSMENT

No pharmacological or toxicological studies or data were submitted as the applicant claimed essential similarity to the reference product which has been approved in the European Community for more than 10 years.

The excipients in the product under consideration and the reference are similar both qualitatively and quantitatively. There were no preclinical objections to the grant of this Market Authorization for Mirtazapine 30 mg tablets.

CLINICAL ASSESSMENT

1. INTRODUCTION

Mirtazapine is a centrally-acting presynaptic alpha 2-antagonist, increasing central noradrenergic and serotonergic neurotransmission, specifically via 5-HT1 receptors, 5-HT2 and 5-HT3 receptors being blocked.

2. BACKGROUND

This Market Authorisation is for 30mg tablets of Mirtazapine, cross-referring to the reference product Zispin 30mg tablets, first licensed to Organon in the UK on 16.03.1994. The bioequivalence study also used Zispin, 30mg tablets, of NV Organon, the Netherlands.

3. INDICATIONS

Mirtazipine is indicated in the treatment of depressive illness.

4. DOSE & DOSE SCHEDULE

Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The tablets should be swallowed without chewing. In adults and the elderly, the recommended starting dose is 15mg daily, the effective dose being usually 15mg-45mg daily, taken preferably as a single night-time dose. There is no evidence of efficacy in children and they should, therefore, not be prescribed.

5. TOXICOLOGY

No formal data are presented and none are required. The innovator product, Zispin, has been used in man for over 10 years without any safety issues. The excipients are well known and have been used widely in pharmaceutical manufacturing.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACODYNAMICS

This is discussed in brief in the introduction.

6.2 PHARMACOKINETICS

Mirtazapine is well absorbed from the gastrointestinal tract, the presence of food having only a small effect on the rate, and no effect on the extent of the absorption. Its absolute bioavailability is about 50%. Steady state plasma levels are attained within 5 days. It is extensively metabolised in the liver, via

demethylation and oxidation, followed by conjugation. Approximately 100% of the orally administered dose is excreted via urine (75.80%) and the faeces (15%) within 4 days.

6.2.1 BIOEQUIVALENCE

A comparative bioavailability study was carried out on mirtazapine 30mg tablets as proposed for marketing using Zispin 30mg tablets (N.V. Organon OSS, Netherlands) as the comparator. The study was conducted in 24 healthy adult males aged 18-50 years. Mirtazapine was measured using a validated LC/MS/MS Method. The following table briefly summarises the bioequivalence study results:

Statistics			**C_{max}**	**AUC $_{o-t}$ (hr.ng/ml)**	**AUC $_{o-inf}$ (hr.ng/mL)**	**T_{max} (hr)***
Test Formulation (Mirtazapine 30mg tablets B.No. MZ3003001)	**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 30mg tablets, B.No. 483175)	**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 %)	**Lntransformed**		105.59	90.95	90.89	-
90 % Confidence Interval	**Lntransformed**	**Lower**	95.03	85.03	84.75	-
		Upper	117.31	97.28	97.47	-
		Power (%)	96	100	100	-

For **T_{max}** instead of mean, median has been used.

As can be seen, the 90% confidence intervals for Mirtazapine 30mg tablets Zispin 30mg tablets transformed parameters C_{max} AUC $_{o-t}$ and AUC $_{o-inf}$ were 95.03-117.31%, 85.03-97.28% and 84.75-97.47% respectively, all well within the accepted 80-125% acceptance range for bioequivalence. Thus the test product is bioequivalent to the reference product.

No serious adverse events were reported.

The biostudy was performed only on male subjects since the pharmacokinetics of Mirtzapine are dependant on gender, in accordance with the Note for Guidance. Likewise, the Note for Guidance provides five requirements all of which must be fulfilled to extrapolate the results of a single strength bioequivalence study to the other strengths to be marketed. The present study and comments from the clinical expert fulfil these requirements.

7. EFFICACY

No new data are presented and none are required for this application. The efficacy of mirtazapine has been well documented.

8. SAFETY

No new data are presented and none are required for this application.
The bioequivalence study did not have any unexpected adverse events

9. EXPERT REPORTS

There is an adequate clinical expert report and a brief but adequate Curriculum Vitae is included, as are those for the preclinical and pharmaceutical experts.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The summary of Product characteristics was amended and is now satisfactory.

11. PATIENT INFORMATION LEAFLET

The patient information leaflet was amended and is now satisfactory

12. LABELLING

The labelling is satisfactory

13. DISCUSSION

Bioequivalence of Mirtazapine 30 mg Tablets and the reference product Zispin has been demonstrated.

Overall Conclusion and Risk/Benefit Analysis

Quality

The quality aspects of Mirtazapine 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.

Pre-Clinical

No new pre-clinical data were presented or were required for this type of application.

Clinical

Bioequivalence of Mirtazapine with the reference product was established.

Risk/Benefit Analysis

The quality of the product, Mirtazapine, is acceptable and the product is essentially similar to the reference product which has a positive risk/benefit assessment. A Marketing Authorisation was granted.

Steps Taken During Assessment

1	The MHRA received the application on 29th July 2004.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on.1st September 2004.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossier 4th July 2005 and 29th March 2006 and on and further information on the clinical dossier on 16th May 2005
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on the 13th July 2005 and 3rd May 2006 and on the clinical dossier 19th May 2005.
5	The applications were determined on 3rd August 2006.

Steps take after procedure

The Market Authorisation was cancelled on 21st April 2007.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mirtazapine 30mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30mg of mirtazapine

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film coated oral tablet

Reddish brown, biconvex capsule shaped film coated tablets with a score line in-between 0 and 9 on one side and ‘A’ debossed on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of depressive illness.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The 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.

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

Mirtazapine has a half-life of 20-40 hours and therefore mirtazapine is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. Mirtazapine 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 four to six months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within two to four weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further two to four 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.

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

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 four to six 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.

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 two weeks, though in some individuals they may be prolonged (two to three 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 INTERACTION 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.

Mirtazapine 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.

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 clinical 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

Pregnancy

The safety of mirtazapine in human pregnancy has not been established.

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg (approx. 3 and 5 times respectively the maximum recommended human dose on the basis of exposure) have revealed no evidence of teratogenic effects. There was, however, in rats an increase in post-implantation loss; there was also an increase in pup deaths during the first three days of lactation (cause of death unknown) and a decrease in pup birth weights. These findings are common with CNS-active drugs at high dose levels in animals.

As the relevance of these findings to humans is not certain the use of mirtazapine during pregnancy is not recommended. Women of child-bearing potential should employ an adequate method of contraception if taking mirtazapine.

Lactation

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of mirtazapine in nursing mothers is not recommended since no human data in breast milk 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 initially impair alertness and concentration. Patients treated with mirtazapine 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:

	Rare (>1/10,000)	**Uncommon (>1/1000)**	**Common (>1/100)**
Blood and the lymphatic system disorders	Reversible agranulocytosis has been reported as a rare occurrence with mirtazapine. (see also section 4.4 'Special warnings and precautions for use')		

Metabolism and nutrition disorders			Increase in appetite and weight gain
Psychiatric disorders	Nightmares/vivid dreams		
Nervous system disorders	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	Dizziness, Headache	
Cardiac disorders	(Orthostatic) hypotension.		
Hepato-biliary disorders		Increases in liver enzyme levels	
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal, connective tissue and bone disorders	Restless legs, Arthralgia/myalgia		
General disorders			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 Precautions for use).

4.9 OVERDOSE

Present experience concerning overdose with mirtazapine alone indicates that 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

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: NO6A
Pharmacotherapeutic group: Antidepressant

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 H1-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 two 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 three to four 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

No special particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Core:

Lactose monohydrate
Hydroxypropylcellulose
Maize starch
Colloidal anhydrous silica
Low-substituted hydroxypropyl cellulose
Magnesium stearate
Purified water

Film-coating:

Opadry Brown 20A56788
(Hydroxypropyl cellulose)
(Hypromellose)
(Titanium dioxide, E171)
(Iron oxide yellow, E172)
(Iron oxide red)
(Iron oxide black)
Purified water

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Keep out of the reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/aluminium foil opaque blister packs containing 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not applicable

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0502

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2006

10 DATE OF REVISION OF THE TEXT

03/08/2006

Labels and Leaflet

PACKAGE LEAFLET

Mirtazapine 30mg 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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours

In this leaflet:

1. What mirtazapine is and what it is used for
2. Before you take mirtazapine tablets
3. How to take mirtazapine tablets
4. Possible side effects
5. Storing mirtazapine tablets

The active substance in the tablets is mirtazapine

The other ingredients are lactose monohydrate, hydroxypropylcellulose, maize starch, colloidal anhydrous silica, low-substituted hydroxypropyl cellulose, magnesium stearate, purified water, Opadry Brown 20A56788 (hydroxypropyl cellulose, hypromellose, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red and iron oxide black.

Mirtazapine 30mg tablets are manufactured by the Marketing Authorisation holder Wockhardt UK, Ash Road North, Wrexham LL13 9UF

1. WHAT MIRTAZAPINE IS AND WHAT IT IS USED FOR

Mirtazapine 30mg tablets are reddish brown, biconvex capsule-shaped, film-coated tablets with a score line between 0 and 9 on one side and 'A' debossed on the other side. They are available in blister packs containing 28 tablets.

Mirtazapine belongs to a group of medicines called antidepressants. Mirtazapine tablets are used to treat depression.

2. BEFORE YOU TAKE MIRTAZAPINE TABLETS

You should not take mirtazapine tablets:

- if you are hypersensitive (allergic) to mirtazapine or any of the other ingredients of mirtazapine tablets
- if you are pregnant or breast-feeding

Women who could get pregnant

Be careful not to get pregnant while taking mirtazapine tablets. You should take adequate precautions by using reliable contraception to ensure that you do not become pregnant.

Special care should be taken:

- if you have epilepsy or brain damage
- if you have liver or kidney problems

- if you have heart problems
- if you have low blood pressure
- if you have diabetes
- if you have prostate problems or difficulty passing water
- if you have glaucoma (pressure in the eye ball)
- if you have schizophrenia
- if you suffer from manic depression
- if you are elderly

Use in children and adolescents under 18 years of age:

Mirtazapine tablets 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 tablets for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed mirtazapine tablets 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 tablets. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of mirtazapine tablets in this age group have not yet been demonstrated.

Taking mirtazapine tablets with food and drink:

It does not matter when you take your mirtazapine tablets in relation to food. You should avoid alcohol while you are taking mirtazapine tablets.

Driving and using machines:

Mirtazapine tablets should not affect your ability to drive or use machines. However, if you are affected do not drive or operate machinery.

Important information about some of the ingredients of mirtazapine tablets:

Mirtazapine 30mg Tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Taking other medicines:

Taking another medicine while you are taking mirtazapine tablets can affect how it or the other medicine works. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those you may have bought yourself without a prescription. Please check with your doctor if you are taking any of the following (or any other medication):

- monoamine oxidase inhibitors (MAOIs) or have taken them within the last two weeks
- benzodiazepines, used to treat anxiety or insomnia
- rifampicin and erythromycin, antibiotics used to treat bacterial infections
- ketoconazole, an antifungal, used to treat fungal infections
- carbamazepine and phenytoin, used to treat epilepsy
- cimetidine, used for stomach ulcers

3. HOW TO TAKE MIRTAZAPINE TABLETS

The usual starting dose in the treatment of depression in adults and the elderly is 15mg a day. This can be increased if necessary to a maximum of 45mg a day, in which case the dose may be split into morning and evening doses. If mirtazapine works for you, you will probably need to take the tablets for four to six months.

Mirtazapine tablets are not recommended in children.

Your doctor will decide the dose that is best for you. Always follow your doctor's instructions completely. Also, follow any instructions or warnings that appear on the label that the pharmacist has put on the pack. If you do not understand, or are in any doubt, ask your doctor or pharmacist.

To obtain a tablet, press on the tablet from the blister (or bubble) side, pushing it through the foil. Do not remove the tablet from the blister until you are ready to take it.

Unless told otherwise, take your tablets with water.

It may be two to four weeks before you begin to feel better. Your doctor will monitor your progress during this time. You should keep taking your tablets even if you feel better and always see your doctor before your tablets run out. If you stop taking your tablets suddenly you may experience dizziness, tingling, headache, anxiety, agitation, nausea and feel unwell and some of your symptoms of depression may come back. When you feel better you should talk to your doctor who will tell you how to reduce your dose. Your dose will be reduced gradually over a six month period.

If you take more mirtazapine tablets than you should:

If you or anybody else takes too many tablets, you should contact your doctor, pharmacist or nearest hospital casualty department immediately. Take this leaflet and any tablets you have left to show the doctor or pharmacist.

If you forget to take mirtazapine tablets:

If you occasionally forget to take a dose do not worry, just take the next dose when it is due. Never double the next dose to make up for the one missed. Do not stop taking the medicine without talking to your doctor first.

4. POSSIBLE SIDE EFFECTS

Like all medicines, mirtazapine tablets can have side effects, especially when treatment is first started. The most common side effects are:

- increase in appetite and weight gain
- swollen ankles and fluid retention
- drowsiness and feeling tired during the first few weeks of treatment.

There is a risk of patients who are depressed harming or killing themselves. This risk is increased when you first start taking the medicine as the medicine takes time to work. The risk is greater in patients who are young adults (aged 18 to 29 years) and in patients who have previously had thoughts about harming or killing themselves. **Please tell your doctor immediately or go to your nearest hospital if you experience suicidal thoughts and thoughts of self-harm.**

Less commonly, dizziness, headache, and changes in liver function have been reported.

Rarely, other effects have been reported which include blood disorders, nightmares or vivid dreams, mania, fits, tremors (shaking), feeling agitated, hallucinations, tingling, numbness, low blood pressure, rash, restless legs, uncontrollable twitching or jerking movements and pain in your joints and muscles.

You should tell your doctor immediately if you develop a fever, sore throat, mouth ulcers or feel unwell or if you develop jaundice (yellow skin and yellow whites of eyes).

Rarely allergic reactions can occur. **You should tell your doctor immediately** if you experience wheezing, difficulty breathing, swelling, rash or itching.

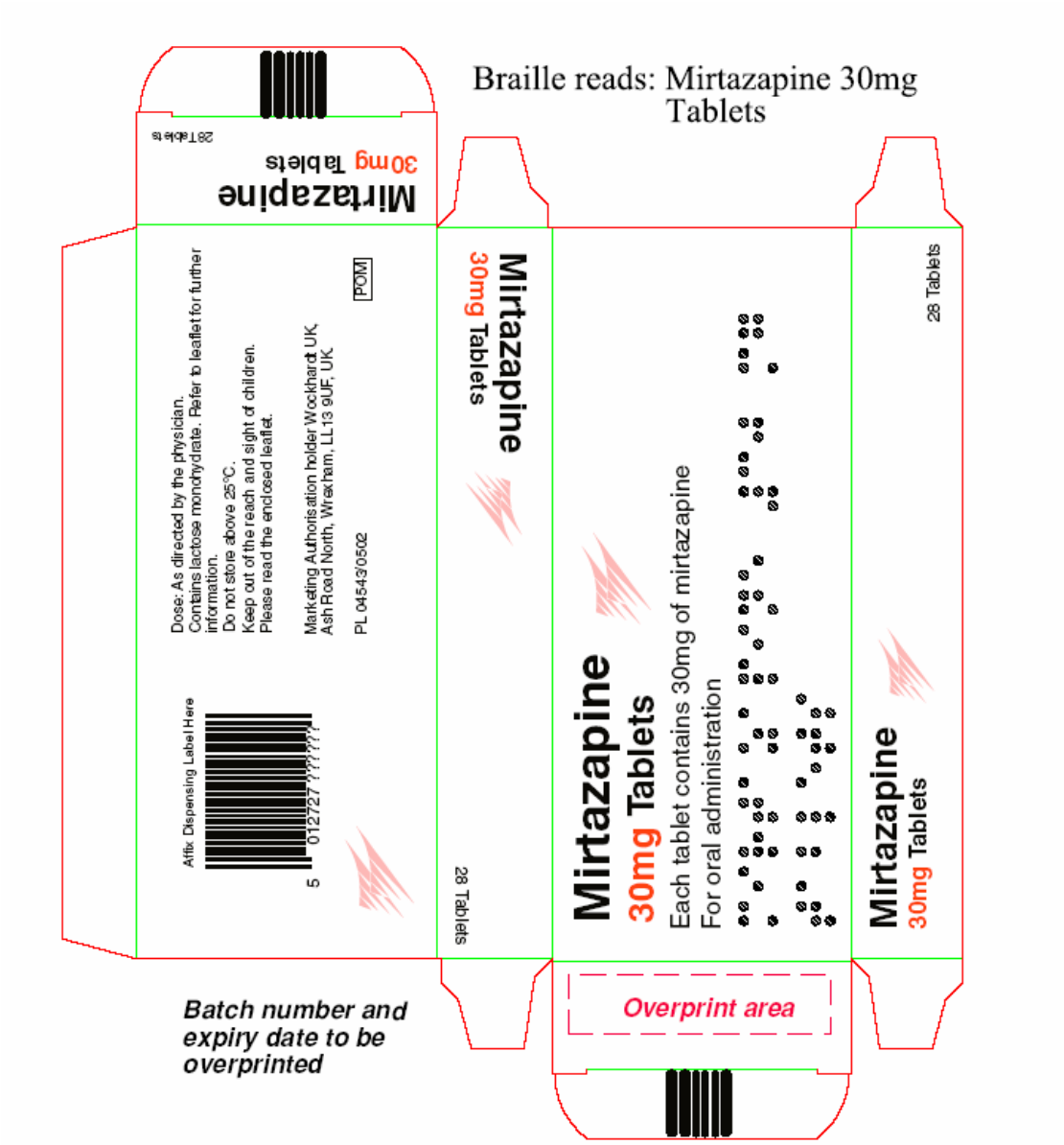
When you stop taking the tablets you may experience withdrawal effects such as dizziness, tingling, headache, anxiety, agitation, nausea and feeling unwell. These should disappear within a few days.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING MIRTAZAPINE TABLETS

Keep out of the reach and sight of children.
Do not store above 25°C.
Do not use after the expiry date stated on the carton.
Do not take mirtazapine tablets if you notice they are discoloured (they should be reddish brown).

This leaflet was last approved on 3rd April 2006


Braille reads: Mirtazapine 30mg Tablets
28Tablets
30mg Tablets
Mirtazapine
Dose: As directed by the physician.
Contains lactose monohydrate. Refer to leaflet for further information.
Do not store above 25°C.
Keep out of the reach and sight of children.
Please read the enclosed leaflet.
POM
Marketing Authorisation holder Wockhardt UK, Ash Road North, Wrexham, LL13 9UF, UK.
PL 04543/0502
Affix Dispensing Label Here
5 012727 ??????
Mirtazapine
30mg Tablets
28 Tablets
Mirtazapine
30mg Tablets
Each tablet contains 30mg of mirtazapine
For oral administration
28 Tablets
Mirtazapine
30mg Tablets
Batch number and expiry date to be overprinted
Overprint area


Mirtazapine 30mg Tablets
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