CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Mirzasna 15 mg, 30 mg and 45 mg, orodispersible tablets Krka d.d., Novo mesto, Slovenia

mirtazapine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1087/001-003/MR
Registration number in the Netherlands: RVG 33280-33282

26 April 2010

Pharmacotherapeutic group:	other antidepressants
ATC code:	N06AX11
Route of administration:	oral
Therapeutic indication:	major depressive episodes
Prescription status:	prescription only
Date of first authorisation in NL:	18 December 2006
Concerned Member States:	Mutual recognition procedure with BG, CZ, DE, DK, EE, FI, IE, NO, PL, RO, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Mirzasna 15 mg, 30 mg and 45 mg, orodispersible tablets from Krka d.d., Novo mesto. The date of authorisation was on 18 December 2006 in the Netherlands. The product is indicated for treatment of major depressive episodes.

A comprehensive description of the indications and posology is given in the SPC.

Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.
The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Remeron SolTab 15 mg, 30 mg and 45 mg orodispersible tablets (NL License RVG 25780-25782), which have been registered since 11 June 2001 by N.V. Organon. Reference is also made to the innovator products Remeron 15 mg, 30 mg and 45 mg film-coated tablets (NL License RVG 16685, 16686 and 18127), which have been registered in the Netherlands since 16 March 1994 (15 and 30 mg) and 16 January 1995 (45 mg). In addition, reference is made to Remeron authorisations in the individual member states, Remergil in Germany (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In BG, the marketing authorization is granted based on article 10(3) 'hybrid application', as Remeron SolTab is not registered in Bulgaria. Reference is made to the Dutch innovator product, as a European reference product.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Remergil Soltab 30 mg orodispersible tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is mirtazapine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to yellowish powder, soluble in methanol, slightly soluble in 0.1 M HCl and practically insoluble in water. Mirtazapine exist as a hydrate form and as an anhydrous form. Only the hydrate form is used.

The Active Substance Master File (ASMF) procedure is used. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The manufacturing of the active substance takes place in two chemical reaction steps, each followed by purification. The process has been adequately described and validated.

Specification
The active substance specification is considered adequate to control the quality. It has been brought in line with the Ph.Eur requirements. The methods are adequately described; mostly general Ph.Eur. methods are used. Batch analytical data demonstrating compliance with the Ph.Eur. specification have been provided for 3 batches of each supplier.

Stability
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance. Based on the data submitted, a retest period could be granted of 2 years when stored in the original package protected from light.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Mirzasna 15 mg, 30 mg and 45 mg are white, round, biconvex orodispersible tablets.

The 3 different tablets strengths are dose-propotional.

The orodispersible tablets are packed in perforated unit dose blister (OPA/Al/PVC//Al foil).

The excipients are: lactose monohydrate, ethylcellulose, mannitol (E421), sorbitol (E420), crospovidone, colloidal hydrated silica, orange juice flavour (containing maltodextrins, modified maize starch), aspartame (E951), magnesium stearate.

Pharmaceutical development

The tablet was designed to develop a stable dosage form with good bioavailability and bioequivalence to the innovator, to achieve a fast disintegration in the mouth, but to prevent drug release in the mouth (by the use of ethyl cellulose), and to achieve an immediate release in gastric media as well as a good taste and mouth feel. Several formulations have been tested. The characteristics are adequately described.
Aspartame is the most suitable sweetener. The handbook on excipients recommends an acceptable daily intake of 40 mg/kg (WHO), in view of the impurity phenylalanine. The amount used in the tablets is far less, so no problems are to be expected. Every tablet batch is routinely tested for dissolution rate and the limit is NLT 80% in 15 minutes. The tablets easily comply with this. This means that the dissolution rate is not a critical parameter for bioavailability. The dissolution rates are essentially similar to the innovator product over the whole pH range 1-6.8. A 3% overage of mirtazapine is used in the formulation, because of the water content in mirtazapine. This is acceptable.

Manufacturing process
Mirtazapine and lactose are blended and granulated with ethyl cellulose dispersed in ethanol. The granulate is then dried, sieved and mixed with the rest of the excipients, after which the orodispersible tablets are compressed. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented for 3 pilot-scale batches and 3 full scale validation batches of each strength from one production site in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur., except the flavouring agent and Pharmaburst C1, for which acceptable in-house specifications are adopted. Pharmaburst C1 consists of mannitol (EP), sorbitol (EP), crospovidone (EP), and hydrated colloidal silica (EP and NF). These specifications are acceptable.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, weight, uniformity of dosage units, disintegration, identification of active substance, related substances, dissolution rate, assay, ethanol, water and microbiological impurity. The methods have been adequately described and validated. Levels of impurities found are given and have been compared with Remergil impurity levels. One of these is found at comparable levels, and other impurities found are below the reporting threshold.
Batch analysis has been performed on three pilot-scale batches of each strength. The batch analysis results show that the finished product meets the proposed specification. The MAH committed to additionally perform the accuracy/recovery for impurity A, impurity B and impurity E at 0.05% and 0.15% relative to the working concentration of mirtazapine in Sample solution. Repeatability of the method within the laboratory and Selectivity of the method will be also tested. The additions of the validation report will be finished by the launch batches.

Stability tests on the finished product
Stability data on the product have been provided for 3 pilot-scale batches of each strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. At least 2 batches of each strength were above 10% of full-scale. The stability results show some increase in water content. The test and the limit are not strictly necessary, for there is no significant increase in the water content and there is no link between water content and other release criteria. The disintegration complies, assay and dissolution show no significant changes or trends. The individual impurities slightly increase, but remain within the limits of specification at all the tested conditions. Based on the results provided, a shelf life was granted of two years with the storage condition '*Store in the original package in order to protect from light and moisture'.* The MAH committed to place the first three production scale batches on stability testing.
The shelf life has been prolonged for the drug product by a type-IB variation to 3 years (NL/H/1087/001-003/IB/006) on 8 October 2008. See also the table on Page 10.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is of vegetable origin, and the lactose used is sourced from milk suitable for human consumption.

II.2 Non clinical aspects

This product is a generic formulation of Remeron SolTab orodispersible tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of mirtazapine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Mirtazapine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Mirzasna 30 mg orodispersible tablets (Krka d.d., Slovenia) is compared with the pharmacokinetic profile of the reference product Remergil Soltab 30 mg orodispersible tablets (Organon, Germany).

The choice of the reference product
The DE innovator product is registered via MRP (NL/H/132/03-05) with the Netherlands acting as RMS. The composition of the DE and NL innovator product is identical, and the DE originator product is therefore acceptable as reference product in the study. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results of the and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 (40 + 4 alternates) healthy male subjects, aged 18-43 years. Each subject received a single dose (30 mg) of one of the 2 mirtazapine formulations. The tablet was placed on the subjects tongue until complete dissolution occurred. After 15 minutes 100 ml of low carbonated water was administered to each subject. The tablets were administered after an overnight fast. Fasting was continued for 6 hours after dosing. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours after administration of the products.

Analytical/statistical methods
Plasma samples were analysed for mirtazapine and the metabolite demethyl-mirtazapine, which is also pharmacologically active. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject did not show up for the second period for personal reasons, one did not show up for the last 5 blood sample collections in period 2, and another subject was found positive for drug abuse (benzodiazepine). These subjects were withdrawn from the study. The remaining 41 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mirtazapine under fasted conditions.

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	536 ± 202	572 ± 208	67 ± 27	1.33 (0.67 - 3.0)	18 ± 8
Reference	518 ± 176	554 ± 181	64 ± 18	1.33 (0.67 - 3.0)	17 ± 7
***Ratio (90% CI)**	1.02 (0.96 - 1.08)	1.02 (0.96 - 1.07)	1.01 (0.93 - 1.09)	-	-
CV (%)	15.6	14.6	21.7	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of demethyl-mirtazapine under fasted conditions.

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	388 ± 109	434 ± 120	26 ± 8	1.35 (1.0 - 4.0)	21 ± 5
Reference	375 ± 114	422 ± 116	26 ± 7	1.67 (1.0 - 3.0)	22 ± 7
***Ratio (90% CI)**	1.03 (0.98 - 1.08)	1.02 (0.98 - 1.07)	0.98 (0.92 - 1.05)	-	-
CV (%)	12.3	11.0	18.3	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of mirtazapine are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of mirtazapine under fasted conditions, it can be concluded that Mirzasna 30 mg and Remergil Soltab 30 mg orodispersible tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the metabolite demethyl-mirtazapine are also in agreement with the range of acceptability, which supports the conclusion of bioequivalence.

According to the SPC the tablet should be put on the tongue until disintegrated. Water or other liquid is not needed to swallow the dose. Although it can be argued that the study design may not be the most critical

design as water was taken after disintegration of the tablet, the MEB finds the current design adequate to compare both formulations. In case no water is used to swallow the tablet, it can be put forward that the outcome it also dependent on the subject's ability to swallow similarly in both study periods and in addition to produce enough and similar amounts of saliva in both periods.

Extrapolation to other strengths
The 15 and 45 mg orodispersible tablet formulations are dose proportional to the 30 mg formulation. The qualitative composition and the ratio between the amounts of active substance and excipients is the same for the 3 orodispersible tablet formulations. The tablets are manufactured by the same manufacturer and the same manufacturing process, and the dissolution profiles are similar (>90% dissolved within 5 min). In addition, it is known that mirtazapine shows linear pharmacokinetics within the recommended dose range. Therefore, the results obtained for the 30 mg formulation can be extrapolated to the 15 and 45 mg formulations.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Mirtazapine was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of mirtazapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product. The MAH committed to update the Pharmacovigilance System in accordance with the latest EU requirements in 2008.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Remeron SolTab orodispersible tablets harmonised via MRP NL/H/132/03-05.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. Following a pilot phase with 2 participants, several sections were revised. Ten participants were involved in each of the two subsequent testing rounds. These rounds did not reveal any problems, and hence no further amendments were made. The test results confirm a sufficient traceability, comprehensibility and usability of the tested PIL.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Mirzasna 15 mg, 30 mg and 45 mg, orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Remeron SolTab 15 mg, 30 mg and 45 mg orodispersible tablets. Remeron SolTab is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other mirtazapine containing products.

The Board followed the advice of the assessors. Mirzasna 15 mg, 30 mg and 45 mg, orodispersible tablets were authorised in the Netherlands on 18 December 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Mirzasna 15 mg, 30 mg and 45 mg with the reference products, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 21 November 2007.

A European harmonised birth date has been allocated (1 September 1994) and subsequently the first data lock point for mirtazapine is 30 September 2010. The first PSUR will cover the period from November 2007 to September 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 21 November 2012.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to place the first three production scale batches on long term stability.
- The MAH committed to perform process validation on 15 mg and 45 mg industrial batches before launching the product.

Pharmacovigilance system

- The MAH committed to update the Pharmacovigilance System in accordance with the latest EU requirements in 2008.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Addition of a secondary packaging site for Germany only.	NL/H/1087/ 001-003/ IA/001	IA	18-2-2008	3-3-2008	Approval	N
Change of batch release arrangements and quality control testing of the finished product; addition of manufacturer responsible for batch release in Germany only.	NL/H/1087/ 001-003/ IA/002	IA	7-5-2008	21-5-2008	Approval	N
Change in the name of the medicinal product in Germany only.	NL/H/1087/ 001-003/ IB/003	IB	19-2-2008	20-3-2008	Approval	N
Adaptation of section 4.4 and 4.8 of the SPC and section 2 of the PIL to PhVWP recommendations for antidepressants and suicidal thoughts and behaviour.	NL/H/1087/ 001-003/ II/004	II	19-3-2008	2-4-2008	Approval	Y, Annex I
Change in the batch size of the finished product.	NL/H/1087/ 001-003/ IA/005	IA	18-7-2008	4-8-2008	Approval	N
Prolongation of the shelf life of the finished product from 2 years to 3 years.	NL/H/1087/ 001-003/ IB/006	IB	8-9-2008	8-10-2008	Approval	N
This variation concerns harmonization of SPC according to the originator's.	NL/H/1087/ 001-003/ IB/007	IB	6-7-2009	6-8-2009	Approval	N
Addition of a manufacturing site for secondary packaging.	NL/H/1087/ 003/IA/008	IA	5-10-2009	19-10-2009	Approval	N

Annex I to the PAR

Type II variation - Antidepressants and suicidal thoughts and behaviour.

Adaptation of section 4.4 and 4.8 of the SPC and section 2 of the PIL to PhVWP recommendations for antidepressants and suicidal thoughts and behaviour.

Section 4.4 - Special Warnings and Special Precautions for Use

Suicide/suicidal thoughts or clinical worsening
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 suicide may increase in the early stages of recovery.

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, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Section 4.8
Where reports of suicidal thoughts or behaviour have been reported with a particular product, this should be reflected in section 4.8

Where a table of adverse drug reactions (ADRs) is included in this section, suicidal ideation and suicidal behaviour should be included in this table – frequency not known and include the following as a footnote:

“Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).”

Where no table of ADRs is included the above text should be inserted in this section.

Revised wording for the Patient Information Leaflet

Thoughts of suicide and worsening of your depression or anxiety disorder
If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away.**
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.