Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Mirtazapine 15 mg, 30 mg and 45 mg orodispersible tablets

(mirtazapine)

UK Licence No: PL 30306/0368-0370

Actavis Group PTC ehf

Lay Summary
Mirtazapine 15 mg, 30 mg and 45 mg orodispersible tablets (mirtazapine)

This is a summary of the Public Assessment Report (PAR) for Mirtazapine 15 mg, 30 mg and 45 mg orodispersible tablets (PL 30306/0368-0370). Mirtazapine 15 mg, 30 mg and 45 mg orodispersible tablets will be referred to as Mirtazapine Orodispersible tablets in this lay summary, for ease of reading.

This summary explains how Mirtazapine Orodispersible tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Mirtazapine Orodispersible tablets.

For practical information about using Mirtazapine Orodispersible tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Mirtazapine Orodispersible tablets and what are they used for?
Mirtazapine Orodispersible tablets are 'generic medicines'. This means that Mirtazapine Orodispersible tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Zispin® Soltab 15mg, 30mg and 45mg Orodispersible Tablets (Organon Laboratories Ltd).

Mirtazapine Orodispersible tablets are used to treat depressive illness.

How do Mirtazapine Orodispersible tablets work?
Mirtazapine Orodispersible tablets contain the active substance mirtazapine, which is one of a group of medicines called antidepressants**.**

How are Mirtazapine Orodispersible tablets used?
Mirtazapine Orodispersible tablets are taken orally at the same time each day.

The usual starting dose is 15 or 30 mg every day. A doctor may advise a patient to increase the dose after a few days to the amount that may be best for them (between 15 and 45 mg per day). The dose is usually the same for all ages. The dose in elderly patients with renal or liver disease may be adjusted by a doctor.

Mirtazapine Orodispersible tablets are best taken as a single dose before going to bed. However a doctor may suggest to split the dose of Mirtazapine Orodispersible tablets – once in the morning and once at night-time. The higher dose should be taken before going to bed.

This medicine can only be obtained with a prescription.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

How have Mirtazapine Orodispersible tablets been studied?
Because Mirtazapine Orodispersible tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Zipsin® 15 mg, 30 mg and 45 mgTablets and Remergil 15 mg, 30 mg and 45 mg Soltab Schmeltztabletten (Organon Laboratories Ltd, The Netherlands), which are equivalent to Zispin® Soltab 15 mg, 30 mg and 45 mg Orodispersible Tablets.. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Mirtazapine Orodispersible tablets?
Because Mirtazapine Orodispersible tablets are generic medicines, their benefits and possible side effects are taken as being the same as those of the reference medicines, Zipsin® 15 mg, 30 mg and 45 mgTablets and Remergil 15 mg, 30 mg and 45 mg Soltab Schmeltztabletten (Organon Laboratories Ltd, The Netherlands).

For further information, please see the package leaflet.

Why are Mirtazapine Orodispersible tablets approved?
It was concluded that, in accordance with EU requirements, Mirtazapine Orodispersible tablets have been shown to have comparable quality and to be bioequivalent to Zipsin® 15 mg, 30 mg and 45 mgTablets and Remergil 15 mg, 30 mg and 45 mg Soltab Schmeltztabletten (Organon Laboratories Ltd, The Netherlands). Therefore, the view was that, as for Zipsin® 15 mg, 30 mg and 45 mgTablets and Remergil 15 mg, 30 mg and 45 mg Soltab Schmeltztabletten (Organon Laboratories Ltd, The Netherlands), the benefits outweigh the identified risks and Mirtazapine Orodispersible tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Mirtazapine Orodispersible tablets?
Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously, as well.

Other information about Mirtazapine Orodispersible tablets
Marketing Authorisations were originally granted in the UK to Olinka UK Limited (PL 08608/0117-0119) on 24 July 2007.

Changes of ownership were granted to Medis EHF (PL 24702/0069-0071) on 16 January 2008 and then to the current Marketing Authorisation Holder, Actavis Group PTC ehf (PL 30306/0368-0370), on 13 July 2011.

The full PAR for Mirtazapine Orodispersible tablets follows this summary. For more information about treatment with Mirtazapine Orodispersible tablets, read the PIL or contact your doctor or pharmacist.

This summary was last updated in October 2016.

Table of Contents

I Introduction

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Mirtazapine 15 mg, 30 mg and 45 mg Orodispersible Tablets (PL 08608/0117-0119) on 24th July 2007. The products are prescription-only medicines (POM).

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the previously approved applications Zispin® Soltab 15mg, 30mg and 45mg Orodispersible Tablets granted to Organon Laboratories Ltd on the 15 July 2003. In turn these applications had demonstrated equivalence to the approved product, Remeron 15mg, 30mg and 45mg tablets (N.V. Organon, Netherlands). The originator products have been authorised in the EU since March 1994 and so the 10-year period of data exclusivity has expired.

The 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.

These applications for Mirtazapine 15mg, 30mg and 45mg Orodispersible Tablets were submitted at the same time and depend on the bioequivalence studies comparing the applicant's 30mg tablets against Zispin® SolTab of the same strength.

Changes of ownership were granted to Medis EHF (PL 24702/0069-0071) on 16 January 2008 and then to the current Marketing Authorisation Holder, Actavis Group PTC ehf (PL 30306/0368-0370), on 13 July 2011.

II Quality aspects

II.1 Introduction

Each tablet contains 15 mg, 30 mg and 45 mg of mirtazapine, as active ingredient.

The excipients present in each tablet are mannitol DC, microcrystalline cellulose, crospovidone, hydroxylpropyl cellulose low substituted, magnesium carbonate heavy, silica colloidal anhydrous, methionine, purified water, magnesium stearate, guar gum, aspartame (E951) and orange flavour.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all the excipients. None of the excipients are novel or contain material of animal or human origin. There are no overages.

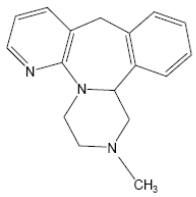
The products are packaged in either blisters composed of aluminium and polyvinyl chloride (PVC) or containers composed of either polypropylene (PP) or high density polyethylene (HDPE). Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The products are packaged in sizes of 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 tablets.

II.2 Drug Substance

Mirtazapine

INN:	Mirtazapine
Chemical Name:	(RS)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino-[2,1-α]pyrido[2,3-c][2]benzazepine 2-methyl-1,2,3,4,10,14b-hexahydro benzo [c]pyrozino[1,2-α]pyrido[3,2-f]-azepine 6-Azamianserin

Structure:



Molecular formula:	$C_{17}H_{19}N_3$
Molecular weight:	265.36g/mol
Physical form:	White to yellowish white crystals or crystalline powder.
Solubility:	Freely soluble in methanol, N,N-dimethyl formamide and ethanol, and practically insoluble in water. Slightly soluble in buffer solutions at pH 2 and pH 4, insoluble at pH 9.
Melting range:	112°C -118°C

The drug substance specification provided is acceptable.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active mirtazapine is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analyses data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated that support the retest period for the drug substance when stored in the proposed packaging.

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

II.3 Medicinal Product

Pharmaceutical development

The objective of the development programme was to formulate safe, efficacious tablets containing 15 mg, 30mg or 45 mg mirtazapine per tablet, that are generic versions of the reference products Zispin® Soltab 15mg, 30mg and 45mg Orodispersible Tablets (Organon Laboratories Ltd). A satisfactory account of the pharmaceutical development has been provided.

Dissolution profiles for all three strengths of the drug product were found to be similar to those for the reference products.

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Product Specifications

The finished product specifications are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the products

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 25°C”, “Store in the original package in order to protect from light and moisture” (for blister) and “Keep the tablet container tightly closed in order to protect from light and moisture” for tablet container.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended.

III Non-clinical aspects

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of mirtazapine are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Mirtazapine 15mg, 30mg and 45mg Orodispersible Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical viewpoint**.**

IV Clinical aspects

IV.1 Introduction

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-antagonistic, 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.

The clinical pharmacology of mirtazapine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this type of application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the Applicant, citing the well-established clinical pharmacology, efficacy and safety of mirtazapine.

IV.2 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 mirtazapine may be decreased as a result of renal or hepatic insufficiency.

Bioequivalence
In support of these applications, the Applicant submitted the following bioequivalence study:

This is a comparative, randomised, single-dose, 3-way Crossover bioavailability study of Pharmaco 30 mg orodispersible Mirtazapine tablets, Organon Laboratories Limited (Zispin®) 30 mg Mirtazapine tablets) and Organon Laboratories Limited (Remergil® Soltab™) 30 mg orodispersible Mirtazapine tablets in 42 healthy adult males under fasting conditions. In each period, subjects were housed from at least 12 hours before dosing until after the 36-hour post-dose events and returned for the 48-, 72-, and 96-hour post-dose events. Single oral 30 mg doses were separated by a washout period of 21 days between each period.

The AUC $_{0-t}$, AUC_{inf}, AUC/AUC_{inf}, C_{max}, t_{max}, half-life, and kel; pharmacokinetic (PK) parameters were calculated for plasma mirtazapine. The analysis of variance (ANOVA) model included sequence, formulation and period as fixed effects and subjects nested within sequence as a random effect. The 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation least-squares means (LSM) resulting from the analyses on the In-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf}, and C_{max}.

A summary of the main pharmacokinetic parameters for mirtazapine are presented in tables 1 & 2 below.

Table 1
Project No: AA19376
Summary of Results – Mirtazapine in Plasma
Pharmacokinetic Parameters
(N = 42)

	ln AUC $_{0-t}$* (ng•h/ml)	ln AUC_{inf}* (ng•h/ml)	ln C_{max}* (ng/ml)	t_{max} (h)	Half-life (h)	kel (h)
Pharmaco (A) Mean CV	615.61 35.1	649.22 35.7	63.79386 41.1	1.298 39.3	23.360 31.7	0.03281 34.4
Organon UK (B) Mean CV	597.61 30.5	632.02 35.7	58.12983 34.6	1.619 53.3	23.565 30.0	0.03247 34.3
Organon Germany (C) Mean CV	593.05 35.4	627.13 35.7	55.64525 38.7	1.660 49.4	23.205 31.5	0.03286 32.4

Table 2. Ratios of LSM% (90% Confidence Intervals) – Mirtazapine in Plasma

Parameter	Pharmaco (A) vs. Organon (Zispin®) (B)	Pharmaco (A) vs. Organon (Remergil® Soltab™)
AUC $_{0-t}$	103.1% (99.4% - 107.0%)	104.1% (100.3% - 108.0%)

AUC_{inf}	102.8% (99.1% - 106.7%)	103.8% (100.1% - 107.6%)
C_{max}	109.8% (102.2% - 118.0%	115.1% (107.1% - 123.7%)

The 90% confidence intervals derived from the analyses of the In-transformed PK parameters AUC_{0-t} and C for mirtazapine and N-demethylmirtazapine in plasma were within the 80% to 125% acceptance range for the Pharmaco (A) versus Organon (Zispin®) (B) formulations and the Pharmaco (A) versus Organon (Remergil® Soltab™) formulations.

Based on these results, the Pharmaco 30 mg orodispersible Mirtazapine tablets are bioequivalent to the Organon Laboratories Limited (Zispin®) 30 mg Mirtazapine tablets and the Organon Laboratories Limited (Remergil® Soltab™) 30 mg orodispersible Mirtazapine tablets.

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

Overall, 45 subjects (100% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment A; 38 subjects (84.4% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment B; and 44 subjects (97.8% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment C.

There were no serious adverse events that occurred during the conduct of this study.

IV.3 Pharmacodynamics

Mirtazapine is a centrally active presynaptic alpha2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-hydroxytryptamine (5-HT) 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.

IV.4 Clinical efficacy

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

IV.5 Clinical 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 other related antidepressants such as amitriptyline. The most common adverse events of mirtazapine are sedation, weight gain and increased appetite.

IV.6 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V User consultation

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised,

easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

VI Overall conclusion, benefit/risk assessment and recommendation

QUALITY

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

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

Based on the results the applicant's Mirtazapine 30 mg orodispersible tablets are bioequivalent to the Organon Laboratories Limited (Zispin®) 30 mg Mirtazapine tablets and the Organon Laboratories Limited (Remergil® Soltab™) 30 mg orodispersible Mirtazapine tablets.

Given that linear pharmacokinetics apply between the 30mg dose and the other doses (15 mg and 45 mg) of mirtazapine formulations, separate bioequivalence studies using the 15 mg and 45 mg tablets have not been considered necessary.

No new or unexpected safety concerns arose from these applications.

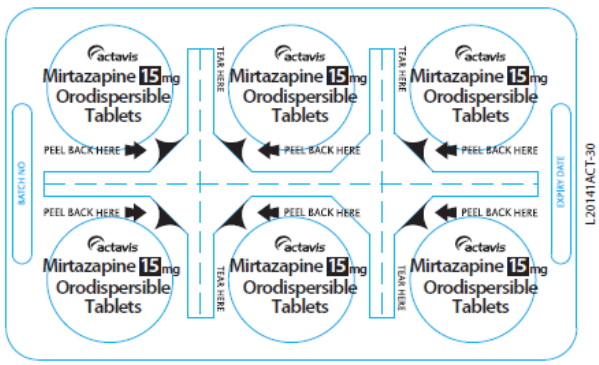
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product.

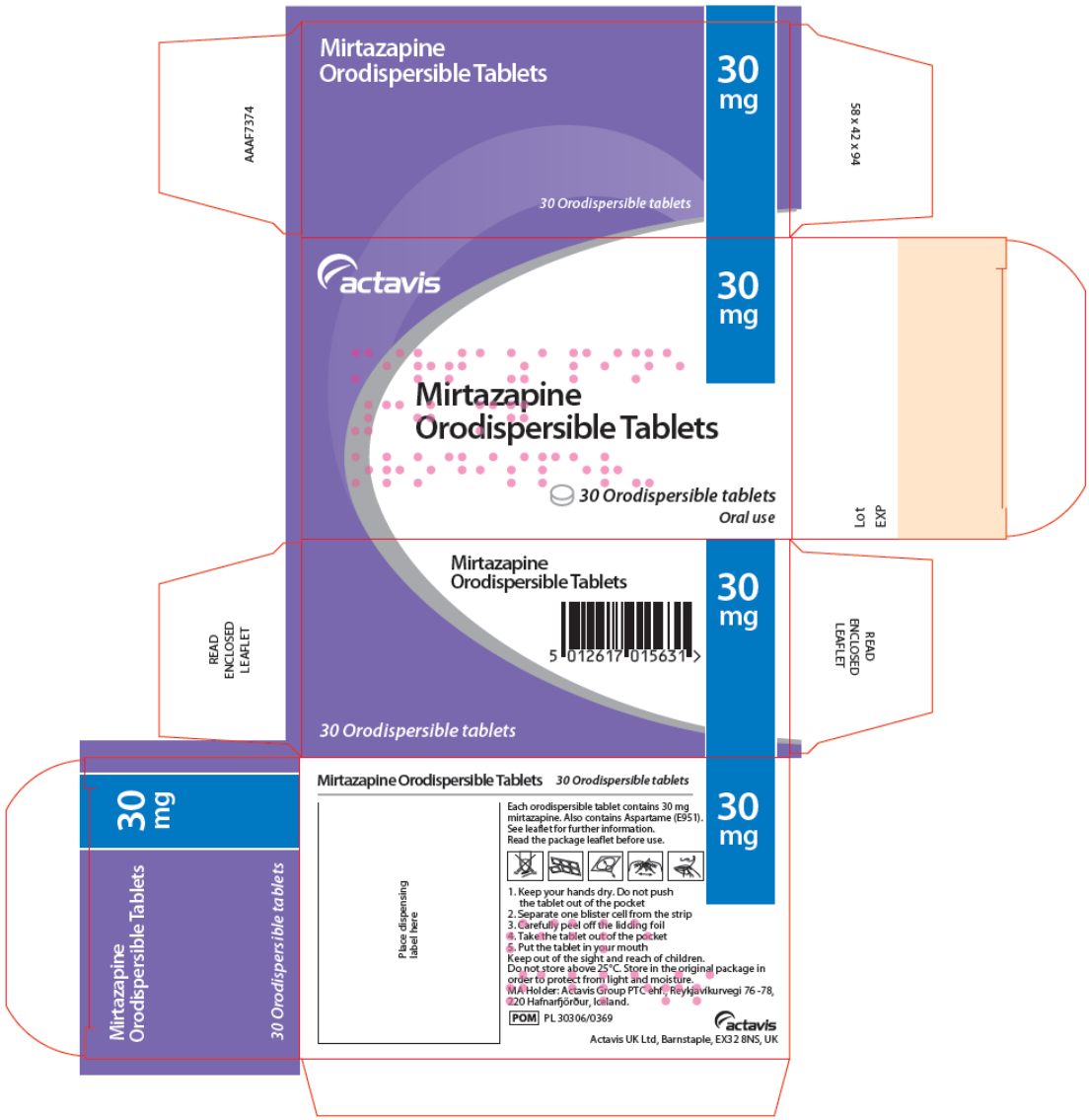
BENEFIT RISK ASSESSMENT

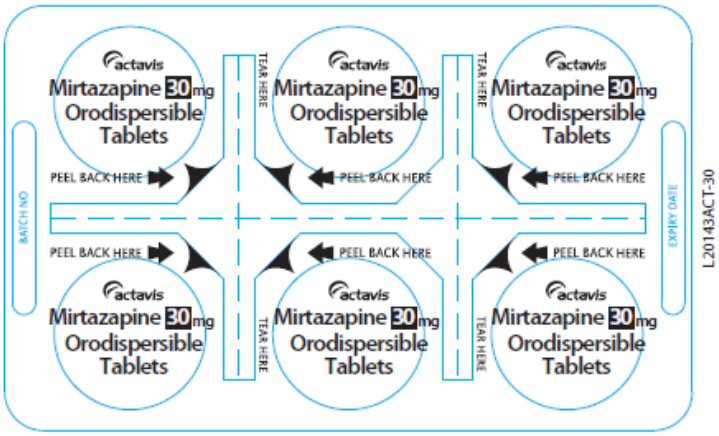
The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with the active ingredient mirtazapine is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

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The current approved UK labelling is presented below:




Mirtazapine Orodispersible Tablets
30 mg
30 Orodispersible tablets
AAAF7374
58 x 42 x 94
actavis
Mirtazapine Orodispersible Tablets
30 Orodispersible tablets
Oral use
LOT
EXP
READ ENCLOSED LEAFLET
5 012617 015631
Mirtazapine Orodispersible Tablets 30 Orodispersible tablets
Each orodispersible tablet contains 30 mg mirtazapine. Also contains Aspartame (E951). See leaflet for further information.
Read the package leaflet before use.
1. Keep your hands dry. Do not push the tablet out of the pocket
2. Separate one blister cell from the strip
3. Carefully peel off the lidding foil
4. Take the tablet out of the pocket
5. Put the tablet in your mouth
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package in order to protect from light and moisture.
MA Holder: Actavis Group PTC ehf., Reykjavikurvegi 76-78, 220 Hafnarfjörður, Iceland.
POM PL 30306/0369
Actavis UK Ltd, Barnstaple, EX32 8NS, UK
Place dispensing label here


actavis
Mirtazapine 30mg Orodispersible Tablets
PEEL BACK HERE
TEAR HERE
BATCH NO
EXPIRY DATE
L20143ACT-30


Mirtazapine Orodispersible Tablets
45 mg
30 Orodispersible tablets
READ ENCLOSED LEAFLET
actavis
Mirtazapine Orodispersible Tablets
30 Orodispersible tablets
Oral use
Lot
EXP
AAAF7378
58 x 42 x 94
Mirtazapine Orodispersible Tablets
30 Orodispersible tablets
Place dispensing label here
Each orodispersible tablet contains 45 mg mirtazapine.
Also contains Aspartame (E951).
See leaflet for further information.
Read the package leaflet before use.
1. Keep your hands dry. Do not push the tablet out of the pocket
2. Separate one blister cell from the strip
3. Carefully peel off the lidding foil
4. Take the tablet out of the pocket
5. Put the tablet in your mouth
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package in order to protect from light and moisture.
MA Holder: Actavis Group PTC ehf., Reykjavikurvegi 76-78, 220 Hafnarfjörður, Iceland.
PL 30306/0370
POM
Actavis UK Ltd, Barnstaple, EX32 8NS, UK

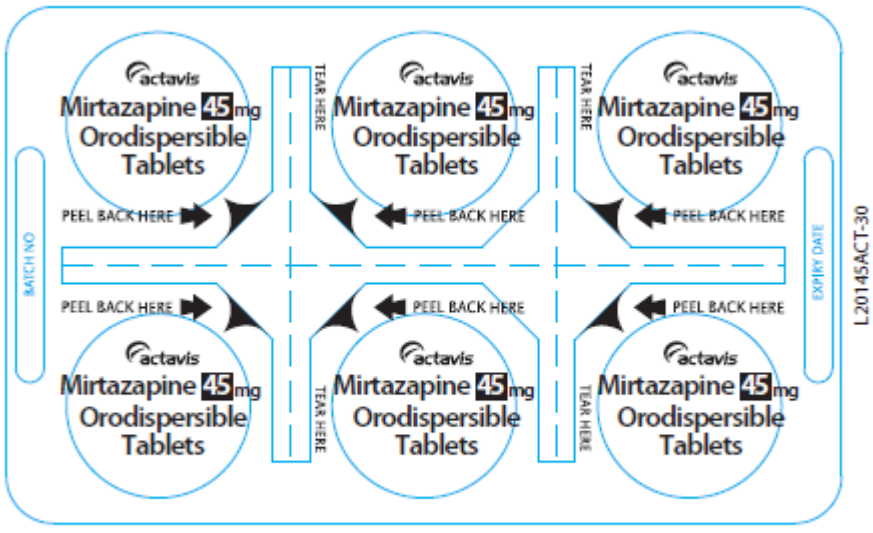

actavis
Mirtazapine 45mg Orodispersible Tablets
PEEL BACK HERE
TEAR HERE
BATCH NO
EXPIRY DATE
L20145ACT-30

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

The following table lists a non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
28/07/2016	IB	To register updated fragments 4.2, 4.4 and 6.1 in line with latest Quality Review of Documents (QRD) template (version 10, 02/2016).	Approved on 24/08/2016

Annex 1

Reference: **PL 30306/0368-0020; PL 30306/0369-0019; PL 30306/0370-0019**

Product: **Mirtazapine 15 mg, 30 mg and 45 mg Orodispersible Tablets**

Marketing Authorisation Holder: **Actavis Group PTC ehf.**

Active Ingredient: **Mirtazapine**

Reason:
To register updated fragments 4.2, 4.4 and 6.1 in line with latest Quality Review of Documents (QRD) template (version 10, 02/2016).

Supporting evidence
The applicant has submitted updated sections of the SmPCs.

Evaluation
The amended sections of the SmPCs are satisfactory.

Conclusion
The variations were approved on 24 August 2016 and the updated SmPC fragments have been incorporated into these Marketing Authorisations. The proposed changes are acceptable.

Decision: Granted