Optimax 500 mg capsules

(L-tryptophan)

PL 11648/0256

UKPAR

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Medicines and Healthcare Products Regulatory Agency

OPTIMAX 500 MG CAPSULES

PL 11648/0256

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Optimax 500 mg capsules. It explains how Optimax 500 mg capsules were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Optimax 500 mg capsules.

For practical information about using Optimax 500 mg capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Optimax 500 mg capsules and what are they used for?
Optimax 500 mg capsules belong to a group of medicines called anti-depressants. Optimax 500 mg capsules are used only in combination with other anti-depressants when these anti-depressants have been used alone in a patient for a period of time but have not been sufficiently effective.

How do Optimax 500 mg capsules work?
Optimax 500 mg capsules contain L-tryptophan, which is found naturally in animal and plant proteins. L-tryptophan is considered an essential amino acid because our bodies can't make it. It is important for the development and functioning of many organs in the body. After absorbing L-tryptophan from food, our bodies convert it to 5-HTP (5-hydroxytryptophan), and then to serotonin, which reduces feelings of anxiety and depression.

How are Optimax 500 mg capsules used?
Optimax 500 mg capsules should be swallowed whole, preferably after food.

The usual starting dose is two capsules, three times a day (morning, midday and evening). This may be increased to four capsules three times a day if considered to be necessary by a doctor.

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

The medicine can only be obtained with a prescription.

What benefits of Optimax 500 mg capsules have been shown in studies?
In tests Optimax 500 mg capsules have been shown to release L-tryptophan in the same way as Optimax 500mg Tablets, which have been used in the UK since 1982. The benefits of Optimax 500 mg capsules are, therefore, taken as being the same as those of the reference medicine.

What are the possible side effects from Optimax 500 mg capsules?
People who take Optimax 500 mg capsules already suffer from depression and/or anxiety disorders and can sometimes have thoughts of harming or killing themselves. These thoughts may be increased when a patient first starts taking antidepressants. Patients who have thoughts of harming or killing themselves should contact their doctor or go to a hospital straight away.

Optimax 500 mg capsules can cause an allergic reaction and patients who suffer from itching, swelling of the face, lips, tongue, mouth or throat or experience shortness of breath, wheezing or difficulty breathing should stop taking the capsules immediately and contact their doctor.

Optimax 500 mg capsules can also cause headache, light headedness or nausea (feeling sick). This medicine also very rarely causes a disease called eosinophilia myalgia syndrome (EMS). Patients who experience symptoms of EMS (fever, muscle or joint pains or a rash) should see their doctor as soon as possible.

For the full list of all side effects reported with Optimax 500 mg capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Optimax 500 mg capsules approved?
The MHRA decided that Optimax 500 mg capsules' benefits are greater than their risks and recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Optimax 500 mg capsules?
Suitable safety information has been included in the summary of product characteristics and the package leaflet for Optimax 500 mg capsules, including the appropriate precautions to be followed by healthcare professionals and patients.
Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Optimax 500 mg capsules
The marketing authorisation for Optimax 500 mg capsules was granted on 7 July 2014.
For more information about treatment with Optimax 500 mg capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in September 2014.

The full PAR for Optimax 500 mg capsules follows this summary.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Optimax 500 mg capsules to Merck Serono Ltd on 7 July 2014. This prescription only medicine (POM) is used for the treatment of treatment-resistant depression after trials of standard antidepressant drug treatments and as an adjunct to other anti-depressant medication.

This application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, as a line extension application. The reference medicinal product for this application is Optimax, 500 mg, tablets (PL 11648/0084) which have been licensed to Merck Serono Ltd since 9 October 2009. Prior to this the tablets were licensed to E. Merck Ltd through Marketing Authorisation PL 0493/5900R. PL 0493/5900R was granted on 11 January 1982.

L-tryptophan is an essential dietary amino acid and, following hydroxylation and decarboxylation, is the major source of 5-hydroxytryptamine (5-HT). L-tryptophan, 5-HT and 5-HT metabolite levels are lower than normal in patients with depression. Administration of L-tryptophan re-establishes the inhibitory action of 5-HT on the amygdaloid nuclei, thereby reducing feelings of anxiety and depression.

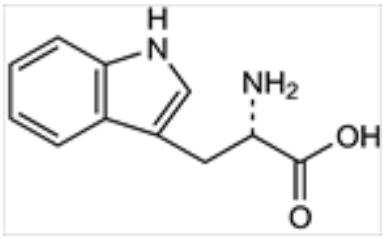
No non-clinical or clinical studies were conducted, which is acceptable given that reference is made to a medicinal product which have been licensed for over 10 years and that satisfactory dissolution data are provided for this medicine which has the same qualitative and quantitative composition in terms of drug substance and a similar qualitative composition in terms of excipients as the reference product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE: Tryptophan

Chemical name: (*S*)-2-amino-3-(1*H*-indol-3-yl)propanoic acid
Molecular formula: $C_{11}H_{12}N_2O_2$
Structure:



Molecular weight: 204.2
CAS registry number: 73-22-3
General properties: White crystalline powder, sparingly soluble in water, slightly soluble in alcohol. Dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides

All aspects of the manufacture and quality control of the active substance are covered by a European Directorate for the Quality of Medicines & HealthCare Certificate of Suitability.

MEDICINAL PRODUCT: OPTIMAX 500 MG CAPSULES

Description and composition
The hard, white capsules have 'OPTIMAX' printed in black on them. Each capsule contains 500 mg L-tryptophan and the excipients povidone K30, sodium starch glycolate, silica colloidal anhydrous, magnesium stearate, gelatin, titanium dioxide (E171), shellac, propylene glycol (E1520), strong ammonia solution (E527), potassium hydroxide and black iron oxide (E172).

All excipients comply with their European Pharmacopoeia monographs with the exception of black iron oxide, which is controlled in line with the NF monograph. In the absence of a European Pharmacopoeia monograph for this excipient this is acceptable.

A Certificate of TSE Suitability has been provided for the gelatin used to make the capsules. None of the other excipients contain materials of animal or human origin.

Pharmaceutical development
The objective of the development programme was to formulate a globally acceptable, stable product that could be used in the place of Optimax 500 mg tablets.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of medicinal product
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container closure system
The capsules are stored in a polypropylene container, with a low-density polyethylene cap. A pack size of 84 capsules has been authorised.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

Stability
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 2 years for capsules stored in an unopened container and of 3 months once the container is first opened.

Bioequivalence/bioavailability
Dissolution data comparing Optimax 500 mg capsules to Optimax 500mg Tablets are provided in place of a bioequivalence study and the two medicinal products were found to have comparable dissolution profiles. In addition, Optimax 500 mg capsules have the same qualitative and quantitative composition in terms of its BCS Class I drug substance and and a similar qualitative composition in terms of excipients as Optimax 500mg Tablets. It is, therefore, reasonable to infer that the bioavailability of Optimax 500 mg capsules does not differ significantly from that of Optimax 500mg Tablets.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Optimax, 500 mg, tablets (PL 11648/0084). The bridging report submitted by the applicant has been found acceptable.

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of L-tryptophan are well-known, no further non-clinical studies are required and none have been provided.

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

Suitable justification has been provided for the non-submission of an environmental risk assessment. As Optimax 500 mg capsules are intended to be used in the place of Optimax 500mg Tablets, a product that is currently marketed, no increase in environmental burden is expected. Thus, the justification for non-submission of an environmental risk assessment is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
Dissolution data comparing Optimax 500 mg capsules to Optimax 500mg Tablets are provided in the place of a bioequivalence study. For further information refer to the quality assessment.

EFFICACY
No new data on efficacy have been submitted and none are required for this type of application.

SAFETY
No new data on safety have been submitted and none are required for this type of application.

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
This is consistent with the SmPC for Optimax 500mg Tablets and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with the PIL for Optimax 500mg Tablets and is satisfactory.

LABELLING
This is satisfactory

MARKETING AUTHORISATION APPLICATION (MAA) FORM
The MAA form is satisfactory from a clinical perspective.

CONCLUSION
The grant of a marketing authorisation is recommended for this application.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Optimax 500 mg capsules 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 this type of application.

CLINICAL

No new clinical data were submitted and none are required for this type of application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for Optimax 500mg Tablets.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Dissolution data have confirmed that Optimax 500 mg capsules can be used in the place of Optimax 500mg Tablets and extensive clinical experience with L-tryptophan is considered to have demonstrated the therapeutic value of the substance. The benefit/risk balance is therefore considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation Application on 21/12/2012
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 3 January 2013.
3	Following assessment of the application the MHRA requested information relating to the dossier on 13 March 2013 and 15 October 2013.
4	The applicant responded to the MHRA's requests providing further information on the dossier on 23 July 2013 and 17 February 2014.
5	The application was granted on 7 July 2014.

SUMMARY OF PRODUCT CHARACTERISTICS

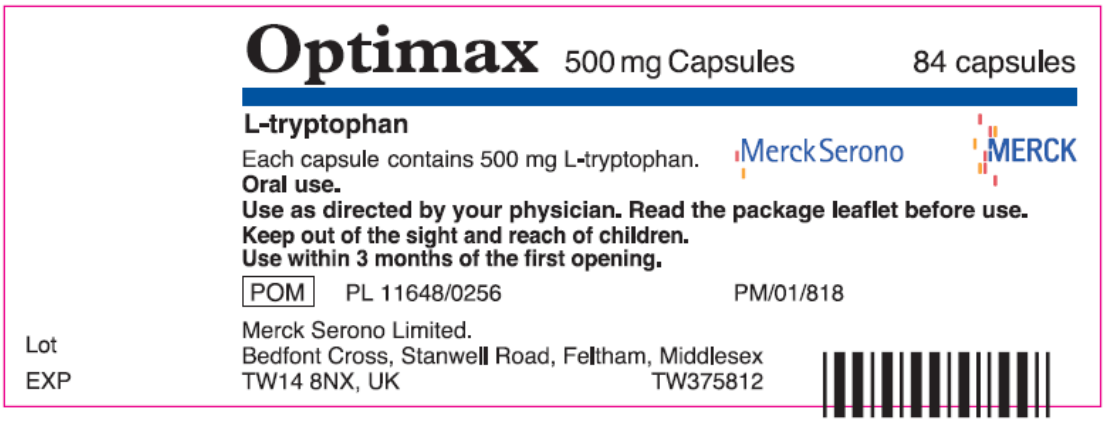
In accordance with Directive 2010/84/EU, the SmPCs for products granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the PILs for products granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING

Label:



Carton: