Public Assessment Report

Decentralised Procedure

Dexamfetamine 5 mg Tablets

Procedure No: UK/H/5007/001/DC

UK Licence No: PL 20477/0034

Kohne Pharma GmbH
LAY SUMMARY
Dexamfetamine 5 mg Tablets
(dexamfetamine sulphate)

This is a summary of the public assessment report (PAR) for Dexamfetamine 5 mg Tablets (PL 20477/0034; UK/H/5007/001/DC). It explains how Dexamfetamine 5 mg Tablets 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 Dexamfetamine 5 mg Tablets.

For practical information about using Dexamfetamine 5 mg Tablets, patients should read the patient information leaflet (PIL) or contact their doctor or pharmacist.

What are Dexamfetamine 5 mg Tablets and what are they used for?
Dexamfetamine 5 mg Tablets are a medicine with a ‘well-established use’. This means that the medicinal use of the active substance of Dexamfetamine 5 mg Tablets has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Dexamfetamine 5 mg Tablets are used to treat attention–deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 - 17 years, when response to another medicine, methylphenidate, is not sufficiently effective.

How do Dexamfetamine 5 mg Tablets work?
Dexamfetamine 5 mg Tablets contain the active substance dexamfetamine sulphate, which is a psychostimulant. This active substance improves activity in parts of the brain, and can help to improve attention span, concentration and reduce impulsive behaviour.

How are Dexamfetamine 5 mg Tablets used?
Dexamfetamine 5 mg Tablets should be swallowed whole with water and taken preferably with, or immediately after, meals. Dexamfetamine 5 mg tablets should be taken at the same time in relation to the meals. The tablets have a score line and can be broken if the patient has difficulty in swallowing them.

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

The prescribing doctor will decide how much of this medicine should be taken, but the usual starting dose is 5 mg (one tablet) taken once or twice a day. The daily dose may then be increased, if necessary, by weekly increments of 5 mg to a maximum of 20 mg for children and adolescents, although 40 mg may be necessary in very rare cases.

Dexamfetamine 5 mg Tablets can only be obtained with a prescription.

What benefits of Dexamfetamine 5 mg Tablets have been shown in studies?
As dexamfetamine sulphate is a well-known substance, and its use in the treatment of ADHD is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of dexamfetamine sulphate in the treatment of ADHD.

In addition, the company (Kohne Pharma GmbH) undertook a bioequivalence study to bridge
their product to the information found in the bibliographic sources relating to the currently approved dexamfetamine sulphate products. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

It was deduced from this study that Dexamfetamine 5 mg Tablets are comparable to another dexamfetamine sulphate product already on the market, Dexamfetamine Sulphate 5 mg Tablets.

**What are the possible side effects of Dexamfetamine 5 mg Tablets?**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur when using Dexamfetamine 5 mg Tablets, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why are Dexamfetamine 5 mg Tablets approved?**

The use of Dexamfetamine 5 mg Tablets in the treatment of ADHD is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Dexamfetamine 5 mg Tablets outweigh the risks and the grant of the marketing authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Dexamfetamine 5 mg Tablets?**

A risk management plan has been developed to ensure that Dexamfetamine 5 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for Dexamfetamine 5 mg Tablets, 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 and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Dexamfetamine 5 mg Tablets**

Denmark, Finland, Ireland, Luxembourg, The Netherlands, Norway, Spain, Sweden and the UK agreed to grant marketing authorisations for Dexamfetamine 5 mg Tablets on 06 August 2014. The marketing authorisation in the UK was granted on 15 September 2014.

The full PAR for Dexamfetamine 5 mg Tablets follows this summary.

For more information about treatment with Dexamfetamine 5 mg Tablets, read the PIL or contact your doctor or pharmacist.

This summary was last updated in November 2014.
# TABLE OF CONTENTS

- **Module 1:** Information about the initial procedure  
  Page 5
- **Module 2:** Summary of Product Characteristics  
  Page 6
- **Module 3:** Patient Information Leaflet  
  Page 7
- **Module 4:** Labelling  
  Page 8
- **Module 5:** Scientific Discussion  
  Page 13
  - I  Introduction
  - II  About the product
  - III  Scientific overview and discussion
  - III.1  Quality aspects
  - III.2  Non-clinical aspects
  - III.3  Clinical aspects
  - IV  Overall conclusion and benefit/risk assessment
- **Module 6:** Steps taken after initial procedure  
  Page 24
Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Dexamfetamine 5 mg Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10a (‘well-established use’)</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Dexamfetamine sulphate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Kohne Pharma GmbH</td>
</tr>
<tr>
<td></td>
<td>Schallbruch 1</td>
</tr>
<tr>
<td></td>
<td>D-42781 Haan</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
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<table>
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<tr>
<td><strong>Day 210</strong></td>
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<tr>
<td><strong>CMDh Arbitration</strong></td>
</tr>
<tr>
<td><strong>CHMP Arbitration started</strong></td>
</tr>
<tr>
<td><strong>CHMP Positive opinion</strong></td>
</tr>
<tr>
<td><strong>Commission Decision (Positive)</strong></td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.
Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 4
Labelling

Carton – Dexamfetamine 5 mg Tablets, 20 tablet pack size

Dexamfetamine 5 mg Tablets
Dexamfetamine sulphate
Each tablet contains 5 mg dexamfetamine sulphate
Contains isomalt (E953).
See leaflet for further information.
To be taken as directed by the physician.

Kohne Pharma GmbH
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42781 Haan
Germany
Telephone: +49 (0) 2129 53 01 55
Telefax: +49 (0) 2129 53 01 0
E-mail: info@kohne-pharma.de

For oral use.
Read the package leaflet before use.
To be taken as directed by the physician.
Keep out of the sight and reach of children.
Do not store above 30 °C.
Store in the original package in order to protect from moisture.
Return unused tablets to the pharmacist.
Carton – Dexamfetamine 5 mg Tablets, 30 tablet pack size
Carton – Dexamfetamine 5 mg Tablets, 50 tablet pack size
Dexamfetamine 5 mg Tablets

Carton – Dexamfetamine 5 mg Tablets, 100 tablet pack size
Blister – Dexamfetamine 5 mg Tablets

Dexamfetamine 5 mg tablets  Dexamfetamine 5 mg tablets
Dexamfetamine sulphate  Dexamfetamine sulphate
For oral use • For oral use • For oral use • For oral use • For oral use
Kohne Pharma GmbH • Kohne Pharma GmbH • Kohne Pharma GmbH
EXP  EXP  EXP  EXP  EXP  EXP  EXP

Dexamfetamine 5 mg tablets  Dexamfetamine 5 mg tablets
Dexamfetamine sulphate  Dexamfetamine sulphate
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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) to Kohne Pharma GmbH for the medicinal product Dexamfetamine 5 mg Tablets. This is a prescription only medicine (POM) indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 years, when response to previous methylphenidate treatment is considered clinically inadequate.

This was an application submitted using the Decentralised Procedure (DCP), with UK as Reference Member State (RMS), and Denmark, Finland, Ireland, Luxembourg, The Netherlands, Norway, Spain and Sweden as Concerned Member States (CMS). The application was made under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

At Day 210 (End of Procedure) the Netherlands considered that the granting of the MA constituted a potential serious risk to public health on the grounds that (i) downgrading the product to second line treatment, along with the proposed Risk Management Plan (RMP) measures, was insufficient to mitigate concerns relating to the perceived potential for misuse and diversion, and (ii) there was insufficient scientific and clinical evidence to support the use of the product as second-line treatment of ADHD. The application was referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), under article 29(1) of Directive 2001/83/EC, on 11 March 2013. However the Member States were not able to reach consensus during the Coordination Group (CMDh) procedure and the UK, as the RMS on the procedure, referred the application to the Committee for Medicinal Products for Human Use (CHMP) under Article 29(4) (EMEA/A-29/1375) on 10 June 2013. The Article 29(4) referral started on 27 June 2013. Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Dexamfetamine 5 mg Tablets outweigh its risks for second-line treatment of ADHD and recommended that the marketing authorisation be granted in all Concerned Member States. The CHMP opinion and assessment report for the referral was adopted by the Committee on 22 May 2014 and the European Commission decision was issued on 06 August 2014. After the national phase, the MA was granted in the UK on 15 September 2014 (PL 20477/0034).

The medicinal product contains the active ingredient dexamfetamine sulphate, which is classified as a sympathomimetic amine with a central stimulant and anorectic activity. Amfetamines increase levels of catecholamine in the synaptic space by blocking reuptake of noradrenaline and dopamine by presynaptic neurons, by releasing dopamine and noradrenaline from dopaminergic neurons, and possibly by inhibiting monoamine oxidase. Dopamine receptors and adrenoreceptors have no affinity for amfetamines as reported. There is also evidence that amfetamines increase release and turnover of serotonin.

As a psychostimulant, dexamfetamine sulphate improves activity in parts of the brain that can help improve attention span, concentration and reduce impulsive behaviour but the precise mechanism of action in ADHD is not fully understood.
Dexamfetamine-containing products have been available in the European Union for nearly half a century and have an established favourable risk-benefit profile. Bibliographic literature data on dexamfetamine sulphate have been submitted to support this application.

In addition to submission of published non-clinical and clinical references the applicant has also performed a bioequivalence study to bridge their product to the information found in the bibliographic sources relating to the currently approved dexamfetamine sulphate products. A randomised, single-centre, single-dose, open-label, two-way crossover Phase I clinical study was submitted to support the application to show bioequivalence of the applicant’s test product Dexamfetamine 5 mg Tablets to a currently approved dexamfetamine sulphate product, Dexedrine Tablets 5 mg (MA holder UCB Pharma Ltd.; PL 00039/0385). The product name for this approved product changed to Dexamfetamine Sulphate 5 mg Tablets, following a change of ownership to the current MA holder, Auden McKenzie (Pharma Division) Ltd. (PL 17507/0188). The clinical study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical efficacy studies were performed for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA Holder has provided a Risk Management Plan (RMP).

The MA holder has provided a satisfactory Environmental Risk Assessment (ERA).
**II. ABOUT THE PRODUCT**

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the product in the Reference Member State</td>
<td>Dexamfetamine 5 mg Tablets</td>
</tr>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Dexamfetamine sulphate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Pharmacotherapeutic group: psychoanaleptics; psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics</td>
</tr>
<tr>
<td>ATC Code</td>
<td>N06BA02</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Tablets 5 mg</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/5007/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
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<td>Member States concerned</td>
<td>Denmark, Finland, Ireland, Luxembourg, The Netherlands, Norway, Spain, Sweden.</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20477/0034</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Kohne Pharma GmbH</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

S. Active substance – Dexamfetamine
rINN: Dexamfetamine sulfate
Chemical name: a.) (S)-α-Methylbenzeneethanamine sulphate
b.) (+)-α-Methylphenethylamine sulfate (2:1)

Structure:

\[
\begin{array}{c}
\text{\text{H}} \\
\text{\text{M}} \\
\text{\text{H2}} \\
\text{\text{N}} \\
\end{array}
\text{.H}_{2}\text{SO}_{4}
\]

Molecular formula: \((\text{C}_9\text{H}_{13}\text{N})_2, \text{H}_2\text{SO}_4\)
Molecular weight: 368.5
Appearance: white or almost white crystalline powder
Solubility: freely soluble in water, slightly soluble in ethanol (96%), practically insoluble in ether

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance dexamfetamine sulphate.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used to contain the active substance. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
P. Medicinal Product  
Other Ingredients  
Other ingredients consist of the following pharmaceutical excipients: isomalt (E953), crospovidone and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development  
The objective of the development programme was to develop a product which has a comparable pharmacokinetic profile with other currently approved dexamfetamine products on the market.

Suitable pharmaceutical development data have been provided for this application.

Manufacturing Process  
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. Process validation has been carried out on pilot scale batches of the finished product and the results are satisfactory.

Control of the Finished Product  
The finished product specification is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System  
The product is packaged in polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters, which are further packed into cartons in pack sizes of 20, 30, 50 and 100 tablets.

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 food.

Stability of the product  
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with storage conditions ‘Do not store above 30 °C’ and ‘Store in the original package in order to protect from moisture’.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

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

A patient information leaflet (PIL) has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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 it contains.

The proposed artwork complies with the relevant statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille.

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

Quality Overall Summary (Expert report)
The quality overall summary has been 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.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of amfetamine and dexamfetamine sulphate are well-known. As amfetamine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

No new pharmaco-toxicological data were found that would change the risk-benefit for dexamfetamine. Amfetamine is a known teratogen and appropriate warnings are included in the proposed SmPC. Studies on genotoxicity and carcinogenicity do not indicate any particular risk for humans.

Regarding related substances, the limits proposed by the active substance manufacturer and finished product manufacturer are essentially in-line with ICH guidance and, therefore, acceptable from a toxicological perspective.

From a non-clinical perspective the SmPC is generally acceptable.

The excipients do not raise any concerns from a non-clinical point of view.
The predicted environmental concentration of dexamfetamine sulphate in the surface water (PEC_{surface} value) is above the threshold of 0.01 µg/l and, therefore, a Phase II environmental fate and effects assessment is required. The applicant has committed to perform a Phase II fate and effects assessment for dexamfetamine sulphate as a post approval follow-up measure.

In conclusion, this application is approvable from a non-clinical point of view.

### III.3 CLINICAL ASPECTS

**Pharmacokinetics**

Dexamfetamine sulphate is a well-known substance and the details of its pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research nor claim any new information in this domain. This is acceptable.

To allow bridging of the information in the published literature to the proposed product a bioequivalence study was undertaken to investigate the comparative bioavailability of the test product Dexamfetamine 5 mg Tablets (Kohne Pharma GmbH) versus a currently approved product already on the market, Dexedrine tablets 5 mg (UCB Pharma Ltd).

**A randomized, single-centre, single-dose, open-label, two-way-crossover Phase I clinical study comparing the bioavailability of the test product versus the reference product in healthy male subjects under fasting conditions.**

Blood sampling was performed pre-dose and up to 48 hours post dose, with a washout period of 1 week.

The main pharmacokinetic results are presented below:

<table>
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<tr>
<th>treatment comparison</th>
<th>metric</th>
<th>confidence interval</th>
<th>point estimate</th>
<th>intra-subject</th>
<th>inter-subject</th>
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<tbody>
<tr>
<td>Test versus Reference</td>
<td>AUC_{0-4} [%]</td>
<td>96.8 – 101.5</td>
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<td>C_{max} [%]</td>
<td>98.9 – 112.1</td>
<td>105.3</td>
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<tr>
<td></td>
<td>AUC_{0-∞} [%]</td>
<td>96.4 – 101.3</td>
<td>98.8</td>
<td>4.29</td>
<td>17.3</td>
</tr>
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</table>

The confidence intervals for AUC and C_{max} were within the acceptance criteria of 80.00 – 125.00 %. Based on these results, the proposed product, Dexamfetamine 5 mg Tablets, can be considered to be bioequivalent with Dexedrine Tablets 5 mg.

**Pharmacodynamics**

Dexamfetamine sulphate is a well-known substance. Its pharmacodynamic actions are relatively well-known despite its mechanism of action in ADHD still remaining unclear. The applicant has presented the summary of the publicly available information regarding the actions of dexamfetamine sulphate in their clinical overview and the proposed SmPC. They have not carried out any original research nor are they claiming any new information regarding pharmacodynamics of dexamfetamine sulphate.
Clinical efficacy
A number of current therapeutic guidelines and standard textbooks list dexamfetamine sulphate as a valid pharmacological treatment option for ADHD. Dexamphetamine sulphate monographs also regularly confirm the claimed information. Furthermore, it is a clear agreement in this type of literature that dexamfetamine sulphate should be used only if the other therapeutic options had been exhausted.

In view of all presented and other publicly available literature, the claim of efficacy can be accepted.

Clinical safety
The applicant has provided a relatively thorough overview of the product safety. Considering nearly half a century of use of the active substance in the proposed indication and in the target population, the safety profile of dexamfetamine sulphate can be regarded as well-known. The bioequivalence study bridges the the proposed product to existing knowledge on safety of the similar products currently available on the market.

Pharmacovigilance system and Risk Management Plan (RMP)
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MA holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dexamfetamine 5 mg Tablets. The following identified and potential risks have been included, as well as missing information:

Important identified risks:
- Drug abuse, misuse and diversion
- Cardiac and cardiovascular disorders, incl. increased blood pressure versus hypertension and increased heart rate, tachycardia, arrhythmias
  Cardiomyopathy
- Increased risk of depression
- Increased risk of aggressive / hostile behaviour
- Psychotic reactions, e.g. hallucination (visual, auditory, skin sensation), mania
- Withdrawal syndrome
- Growth and development, e.g. anorexia
- Serious skin reaction

Important potential risks:
- Ischaemic / Serious cardiovascular events, e.g. myocardial infarction, sudden death, cyanosis, QT prolongation
- Cerebrovascular disorders e.g. stroke (ischaemic and haemorrhagic)
- Migraine
- Raynauds syndrome
- Suicidal ideation
- Tics / Tourettes / dystonias
- Repetitive behaviours
- Seizures
- Growth and development; e.g. sexual maturation, neonatal growth (via lactation)
- Neonatal toxicity e.g. cardio-respiratory toxicity
- Carcinogenicity
- Off-label use

**Missing information.**
- Long-Term Safety (cardiovascular, growth, neurological, cognition and psychotic)
- Pregnancy

**Discussion on the clinical aspects**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The publicly available bibliographic data does support the claim of well-established use for the sought indication in the target population. The applicant has also performed a bioequivalence study effectively bridging their product to the information found in the bibliographic sources relating to the currently approved dexamfetamine sulphate products.

The indication applied for is Attention-Deficit/Hyperactivity Disorder (ADHD) in children from 6 years of age and adolescents as part of a comprehensive treatment programme, if other medicinal and non-medicinal therapeutic measures are not sufficiently efficacious.

The grant of a marketing authorisation is recommended for this application.
OPINION OF THE COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

The Committee for Medicinal Products for Human Use (CHMP) considered the notification of the referral triggered by the United Kingdom under article 29(4) of Directive 2001/83/EC. The Netherlands considered that the granting of the marketing authorisation constitutes a potential serious risk to public health on the grounds that there were concerns as to:

(i) whether downgrading the product to second line treatment, along with the proposed RMP measures, were sufficient to mitigate concerns relating to the perceived potential for misuse and diversion, and
(ii) whether sufficient scientific and clinical evidence exists to support the use of the product as second-line treatment of ADHD.

The Committee reviewed all the data submitted by the applicant in support of the efficacy of dexamfetamine sulphate in the second-line treatment of ADHD, and the proposals for mitigation of the risk of misuse and diversion.

The Committee was of the opinion that dexamfetamine sulphate has a mechanism of action different from that of the methylphenidate and that the available data is supportive of the efficacy of dexamfetamine sulphate in treatment of ADHD.

The Committee was also of the opinion that the proposed risk minimisation measures were appropriate to mitigate the risks of misuse and diversion. A commitment was required by the MA holder to undertake a drug utilisation study to follow the use of prescribed dexamfetamine sulphate in the European Union using multiple data sources. Furthermore, the Committee requested that a post authorisation safety study (PASS) be conducted to evaluate the long-term safety profile of dexamfetamine sulphate in children with ADHD, specifically targeting key issues, such as cardiovascular events, growth and psychiatric-related adverse events.

Therefore, the CHMP was of the opinion that the benefit/risk ratio of Dexamfetamine 5 mg Tablets, and associated names, is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation conditional on updates to the RMP and amendments to the SmPC and PIL, in addition to undertaking the DUS and PASS listed above.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Dexamfetamine 5 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 an application of this type.

CLINICAL
With the exception of the bioequivalence study, no new clinical data were submitted in support of this application.

As per the results of the bioequivalence study, the proposed product is considered bioequivalent with Dexedrine® Tablets 5 mg (UCB Pharma Limited). This allows bridging of the information in the published literature to the proposed product.

No new or unexpected safety concerns arose from this application.

The active substance has been used in the proposed indication and in the target population for more than half a century. The clinical overview adequately summarises the published literature and it is possible to conclude that safety profile of dexamfetamine sulphate is well-known. The bioequivalence study bridges the proposed product to existing knowledge on safety of the similar products currently available on the market.

The SmPC, PIL and labels are acceptable form a clinical perspective. The PIL is consistent with the details in the SmPC and in-line with the current guidance. The labelling is also in line with the current guidance.

BENEFIT/RISK ASSESSMENT
Clinical pharmacology, safety and efficacy of dexamfetamine sulphate is well-known. In view of the information provided in the dossier and applicant’s responses to additional questions raised during the procedure, the risk/benefit balance can be extrapolated from the similar dexamfetamine sulphate products already available on the market to the proposed product. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
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