Title	Drug utilization study of dexamfetamine in European countries
Protocol version identifier	2.1
Date of last version of protocol	08 September 2015
EU PAS register number	ENCEPP/SDPP/7778
Active substance	Dexamfetamine (ATC code: N06BA02)
Medicinal product	On 06 May 2015, the name changes in some European Countries were approved (UK/H/5007/001/IB/001). UK: Amfexa 5 mg Tablets DK: Attentin ES: pending FI: Attentin 5 mg tabletti IE: Tentin 5 mg Tablets LU: Attentin NL: Amfexa 5 mg tabletten NO: Attentin 5 mg tabletter SE: Attentin 5 mg tablett
Product reference	Following change of ownership from Kohne Pharma to MEDICE: UK: PL 11243/0021 DK: 49372 ES: pending FI: 30066 IE: PA 1555/3/1 LU: 201420350 NL: RVG 110336 NO: MTnr. 11-8529 SE: 46616
Procedure number	EMEA/H/A-29/1375 (previous) EMEA/H/N/PSP/0021 (current)
Marketing authorisation holder (MAH) and sponsor company	MEDICE Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany Telephone: +49 (0) 2371 937-0
Joint DUS	*No*

Research question and objectives	• to describe how dexamfetamine is prescribed in Europe • to evaluate off-label use in Europe • to collect data on abuse, misuse, diversion and dependence related to dexamfetamine
Country(-ies) of study*	Denmark, Finland, Germany, Ireland, Norway, Spain, Sweden, The Netherlands and the UK
Author	IMS Health

* Luxembourg is not included as there is no suitable database for the study available

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2. List of abbreviations

ADHD:	Attention Deficit Hyperactivity Disorder
ATC:	Anatomic Therapeutic Classification
CHMP:	Committee for Medicinal Products for Human Use
EMA:	European Medicines Agency
EMCDDA:	European Monitoring Centre for Drugs and Drug addiction
EMR:	Electronic Medical Record
ENCePP:	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP:	General Practitioner
ICD 10:	International Classification of Diseases 10th Revision
MAA:	Marketing authorization applicant
OTC:	Over the Counter
PRAC:	Pharmacovigilance Risk Assessment Committee
RMP:	Risk Management Plan
SAP:	Statistical Analysis Plan
WHO:	World Health Organization

3. Responsible parties

Sponsor:

MEDICE Arzneimittel Pütter GmbH & Co. KG

Kuhloweg 37

58638 Iserlohn

Germany

Project manager: (PRIVACY)

Contractor: IMS Health

IMS HEALTH GmbH & Co. OHG
Erika-Mann-Str.5
80636 München
Germany

IMS is a partner centre of the ENCePP scientific network which is coordinated by the European Medicines Agency. IMS is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

Project team:

The project will be managed by the IMS Centre of Excellence (COE) in Epidemiology, Safety and Risk Management. As team members are likely to change over the project period of 5.5 years, no individual names are listed here. All project tasks will be performed by adequately qualified staff, including experienced senior project coordinators, epidemiologists, and medical experts.

Statistical analysis will be conducted by IMS Health in-house experts. These teams have many years combined experience of analyzing and drawing statistically robust findings from longitudinal and cross-sectional patient data.

4. Abstract

Title

Drug utilization study of dexamfetamine in European countries

Rationale and background

Dexamfetamine is on the market in Germany and UK. The MAA at that time, Kohne Pharma, planned to launch dexamfetamine (Dexamed® and associated names) in Denmark, Finland, Ireland, Luxembourg, Norway, Spain, Sweden, and The Netherlands. The planned study is part of the risk management plan (RMP) for dexamfetamine which had been proposed by the MAA. After the consideration of the RMP for dexamfetamine by PRAC in April 2013, EMA/CHMP had recommended expanding the drug utilization study (DUS) to monitor for reports of abuse and/or overdose by considering the data from poison control centers and drug monitoring centers. The MAA has agreed to follow this recommendation. The present study protocol is in line with the synopsis of the DUS and the strategy for data collection on abuse, misuse, diversion and dependence appended to the RMP as requested by the CHMP in November 2013.

Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Dexamed outweigh its risks for second-line treatment of ADHD and recommended that the marketing authorisation be granted in all concerned Member States. The European Commission issued a decision on 06 August 2014, with the obligations to update the RMP section VI.2.5, Annex 2 and 7, and Part III within 3 months of the EU-Commission decision, to provide final protocols for the DUS and PASS.

In December 2014, the marketing authorisation has undergone a change of ownership to MEDICE, which was completed in January 2015.

On 06 May 2015, the name changes in some European Countries were approved (UK/H/5007/001/IB/001). "Dexamed" as name is not any longer used.

Research question and objectives

This is a retrospective database analysis to provide data on drug utilization on an annual basis for up to 5 years. Objectives are

- to describe how dexamfetamine is prescribed by physicians in Europe
- to evaluate off-label use by physicians in Europe, defined as;
    - o prescription for an indication other than ADHD
    - o Age <6 years or ≥18 years
    - o Prescribed overdose
- to collect data on abuse, misuse, overdose, diversion and dependence related to individual dexamfetamine use

Study design

This is a retrospective database analysis combined with a data collection from drug poison control and drug monitoring centers and other sources plus a literature review.

Population

For the DUS patients who have been prescribed dexamfetamine at least once during the study period.

Variables

Patient information (age, gender, diagnosis associated with the dexamfetamine prescriptions), prescriber specialty, prescription derived variables (average daily dose, percentage of patients above maximum dose; if available co-prescriptions, new/switch/repeat prescriptions, discontinuation, co-morbidities); for IMS® Disease Analyzer and CPRD data on duration of exposure (treatment persistence), dependence syndrome (ICD 10 F15.2) during dexamfetamine exposure.

Data sources

Drug utilization data will be extracted from cross-sectional prescription databases (MIDAS Prescribing Insights central database and Prescribing Insights local databases) for Finland, Germany, Spain, The Netherlands and UK; from longitudinal patient level databases (IMS® Disease Analyzer Germany, CPRD UK) and from National registries for Denmark, Norway and Sweden. A respective database for Luxembourg is currently not available.
Drug monitoring and poison control centers in Denmark, Germany, Netherlands, Norway and UK will be contacted and ask data on abuse, misuse, overdose, diversion and dependence related to dexamfetamine. In addition, a search will be conducted in other data sources in Europe accompanied by bibliographic and grey literature search.

Study size

For the DUS, data of all patients with at least one record of dexamfetamine prescription in the databases during the reporting period will be used.

Data analysis

For the DUS, the analysis of databases will be done descriptively. A detailed statistical analysis plan (SAP) will be agreed on prior to the start of the analysis.

Information from drug monitoring centers and poison control centers, other databases, literature and internet searches will be summarized per reporting period and compared with the findings from previous reports.

Milestones

Annual reports will be written over a period of 5 years. The annual report will include the results of the retrospective database analysis and the information retrieved from drug poison control and drug monitoring centers and other sources as well as the literature review.

5. Amendments and updates

Version 1.0, abbreviated version, was submitted and assessed during the MA application.

Version 1.1 was submitted as condition of the marketing authorisation, including full description of study design and milestones.

Version 2.0 reflects changes made in response to comments from the PRAC assessment report (23 April 2015).

Version 2.1 reflects changes made in response to comments from the PRAC assessment report (21 August 2015).

6. Milestones

Milestone	Planned date*
Start of data collection	Q3 2015*
End of data collection	Q4 2019*
First report of study results	Q4 2016*
Second report of study results	Q4 2017*
Third report of study results	Q4 2018*
Fourth report of study results	Q4 2019*
Final report of study results	Q4 2020

**actual dates will depend on the launch dates of Attentin/Tentin/Amfexa; the data collection period will start when data for dexamfetamine use can be collected for at least three European countries*

The progress reports will be submitted as part of the PSURs to the national competent authorities in which the PASS is conducted according to Module VIII and with any risk management plan updates, where applicable. The progress reports will include overall market availability based on sales data for each country involved in the study as provided in the corresponding PSUR.

The progress reports will be presented in each PSUR of the marketing authorisation involved in the original DCP and additionally Germany, as this country-specific data will be used as well.

The study will be commenced for all involved countries in the same year 2015 with a 5 year study period. Data for analysis will be included for each single country individually based on launch data within the 5 year study period which means that for some countries the presented data might be less than for other countries. Table 1 in the protocol depicts the planned launch dates and the consideration of the country-specific data in the 5 subsequent reports according to the launch sequence.

Table 1: Launch and reporting date by country

Country[1]	Launch date of Dexamed® (and associated names)	Report 1 Q3 2016	Report 2 Q3 2017	Report 3 Q3 2018	Report 4 Q3 2019	Final Report Q4 2020
Denmark	Q2 2015	x	**	**	**	**
Finland	Q3 2015	**	**	**	**	**
Germany	Already marketed (trade name Attentin®)	x	x	x	x	x
Ireland	Q3 2015	**	**	**	**	**
Netherlands	Q3 2015	**	**	**	**	**
Norway	Q3 2015					

		**	**	**	**	**
Spain	tbd	**	**	**	**	**
Sweden	Q3 2015	**	**	**	**	**
UK	Already marketed (trade name: Dexedrine®)	x	x	x	x	x

[1]no suitable database for Luxembourg available;
X= data to be included in the report; **data will be included in the report if available (expected for the first time in the year after the country specific launch)

7. Rationale and background

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a developmental disorder (1). It is primarily characterized by the co-existence of attentional problems and hyperactivity, with each behaviour occurring infrequently alone and several inattentive or hyperactive-impulsive symptoms present prior to age 12 (2). ADHD is the most commonly studied and diagnosed psychiatric disorder in children, affecting about 3 to 5 percent of children globally (3-5) and diagnosed in about 2 to 16 percent of school aged children (4). ADHD is a lifetime disorder (6) with 30 to 50 percent of those individuals diagnosed in childhood continuing to have symptoms into adulthood (7). These symptoms include significant social, emotional and academic problems, low self-esteem, poor peer relationships, delinquency and substance abuse (4).

The exact causes of ADHD are not known, although many studies suggest that there is a large genetic influence (8). Like many other psychiatric illnesses, ADHD results from a combination of factors. In addition to genetics, scientists are investigating possible effects of environmental factors, brain injuries, nutrition and the social environment on the development of ADHD (9).

Treatment of ADHD

Currently available treatments focus on reducing the symptoms of ADHD and improving functioning. Treatments include medication, various types of psychotherapy, education or training, or a combination of treatments.

Most commonly, ADHD is treated with stimulant medications, which are designed to have a calming effect on children with ADHD. In general, their mechanism of action is on catecholaminergic neurons in the brain and ultimately leads to an increase of extracellular dopamine and norepinephrine levels in the prefrontal cortex (10). Alternatively, if stimulant medication is unsuitable, some ADHD patients are treated with non-stimulant medication (e.g. atomoxetine; 11).

Different types of stimulant medications, such as methylphenidate (eg. Ritalin®, Concerta®), lisdexamfetamine (e.g. Elvanse®) and dexamfetamine (e.g. Attentin®) are available.

Non-medical use and diversion of stimulants

Non-medical use and diversion of stimulants is a known problem (12). A systematic literature review found rates of past year non-prescribed stimulant use to range from 5% to 9% in grade school- and high school-age children and 5% to 35% in college-age individuals. Lifetime rates of diversion ranged from 16% to 29% of students with stimulant prescriptions (13). The results are based on data from US and Canada. According to a German study, the illicit use of stimulants for cognitive enhancement is significantly higher than non-medical use of prescription stimulants

among pupils and students (14). Lifetime prevalence for use of prescription stimulants (methylphenidate, amphetamines) for cognitive enhancement was 1.6% in pupils and 0.8% in students, whereas lifetime illicit use of stimulants (amphetamines, cocaine, ecstasy) for cognitive enhancement was reported to be 2.4% and 2.9%, respectively.

In US, poison control center data are used to describe the non-medical use and diversion of prescription stimulants (15,16). A current published analysis on extended-release amphetamine and extended-release oral methylphenidate has used the RADARS® system poison center program and the RADARS® system drug diversion program (16). A similar reporting system is currently not available in European countries.

Rationale of the current study

Kohne Pharma GmbH submitted an application for approval of Dexamed (dexamfetamine sulphate) 5 mg tablet in a decentralised procedure on the basis of well-established use, i.e. bridging to the literature data of other amphetamine products based on PK data. In the procedure, UK acted as Reference Member State with eight Concerned Member States: Denmark, Finland, Ireland, Luxembourg, the Netherlands, Norway, Spain, and Sweden.

The DCP started on 29 August 2011.

On Day 210 (10 March 2013) of the DCP, most of the CMS agreed with the RMS conclusion that the application could be approvable except the Netherlands which raised a potential serious risk to public health (PSRPH) regarding insufficient data to support efficacy in a second line indication and lack of safety regarding abuse potential. A referral was thus triggered at the CMD(h) and was started on 8 April 2013. In the CMD-referral procedure, a trend-vote revealed a majority (21 vs 5 member states) to endorse the RMS position to consider the application approvable for the second-line indication. NL, BE, FR, HU en SK disagreed. The RMS considered abuse potential to be covered by the RMP and stressed that national distributing restrictions may be implemented if necessary.

The procedure was referred to the CHMP on 10 June 2013.

During the CHMP meeting in June 2013, the Committee appointed Ian Hudson UK as Rapporteur and Barbara van Zwieten-Boot as Co-Rapporteur and adopted a List of Questions and the procedure started on 27 June 2013.

The responses to the CHMP LoQ were received from the applicant/MAA on 30 September 2013. The conclusion of the Rapporteur's report was that based on the submitted data provided by the applicant, NL still considers the benefit-risk balance to be negative. According to NL, the applicant has not properly addressed the potential abuse and dependence of this product as well as the clinical evidence that the product is effective as second line treatment in ADHD is not demonstrated. Therefore the original objections are considered unresolved.

In November 2013, the UK issued an AR on the response on the LoQ dated, 6 November 2013: The applicant should demonstrate or justify that the benefit/risk of the product is positive, taking into account:

- the risk for abuse and dependence
- the risk minimization measures taken, i.e., second line, RMP measures
- the clinical evidence that the product is effective as second line treatment in ADHD

The conclusion of the Rapporteur was that the applicant has adequately addressed the CHMP Rapporteur's opinion that the proposed product is approvable. Based on the assessment of the Co-Rapporteur and the comments of the MSs, a list of outstanding issues (questions in LoOI) dated 21 November 2013 was sent to the applicant:

1. Discuss in detail the proposed strategy for data collection on abuse, misuse, diversion and depend-ence.

2. Submit synopsis of the protocols of the proposed post authorisation safety study (PASS) and drug utilisation study (DUS).

3. Submit any available data on abuse, misuse, overdose, diversion and dependence of dexamfeta-mine, particularly in Member States where dexamfetamine-containing products are currently ap-proved. The risk of abuse, misuse, overdose, diversion and dependence of dexamfetamine with re-spect to other ADHD treatment options should be discussed by the applicant.

The response to the CHMP LoQ was received from the applicant on 10 February 2014. The conclusion of the Rapporteur was that the presented evidence was sufficient to conclude the safety and efficacy of the product when used as intended. They were also of opinion that the proposed risk minimisation measures including its downgrading to the second line treatment were evidently (according to German and UK experience) sufficient to deal with the perceived risks of misuse of the product. They concluded that the product is approvable. Whereas the Co-Rapporteur considered based on the outline of epidemiological and experimental literature, the abuse-potential of (immediate relased-) dexamfetamine to be a serious risk for public health.

On 12 May 2014, SAG Psychiatry meeting took place, and the opinion of the SAG was forwarded to the CHMP. On 20 May 2014, at the CHMP plenary meeting, the applicant summarized their planned actions and the current available data on the abovementioned issues.

On 22 May 2014, the European Medicines Agency completed an arbitration procedure following a disagreement among Member States of the European Union (EU) regarding the authorisation of the medicine Dexamed (dexamfetamine sulphate). The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Dexamed outweigh its risks, and the marketing authorisation can be granted in the United Kingdom and in the following countries: Denmark, Finland, Ireland, Luxembourg, the Netherlands, Norway, Spain and Sweden.

Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Dexamed outweigh its risks for second-line treatment of ADHD and recommended that the marketing authorisation be granted in all concerned Member States. The European Commission issued a decision on 06 August 2014, with the obligations to update the RMP section VI.2.5, Annex 2 and 7, and Part III within 3 months of the EU-Commission decision, to provide final protocols for the DUS and PASS, to provide final study results of the PASS by the latest Q2 2020.

In December 2014, the marketing authorisation has undergone a change of ownership to MEDICE, which was completed in January 2015.

On 06 May 2015, the name changes in some European Countries were approved (UK/H/5007/001/IB/001). Dexamed is not any longer used.

In this drug utilization study, retrospective data from patient-level and prescription databases covering the time period from Q3 2015 to Q4 2019 (up to 5 years post product launch) will be analyzed and presented in annual reports. Furthermore, information on abuse, misuse, overdose, diversion and dependence associated with dexamfetamine gathered by active examination of different sources will be added to the annual reports.

This protocol specifies the objectives of the study, describes the methodology & data sources, outlines the approach for both the DUS and the data collection strategy on abuse, misuse, overdose, diversion and dependence and details the tasks and timelines for the project.

8. Research question and objectives

The study's overall objective is to design and implement a drug utilization study for the next 5 years with dexamfetamine and provide data on an annual basis in up to 9 European countries. The planned study is part of the risk management plan for dexamfetamine.

The specific objectives are:

- to describe how dexamfetamine is prescribed by physicians in Europe

- to evaluate off-label use by physicians in Europe, defined as;
    - o prescription for an indication other than ADHD
    - o Age <6 years or ≥18 years
    - o Prescribed overdose
- to collect data on abuse, misuse, overdose, diversion and dependence related to individual dexamfetamine use

In order to address the objectives two different types of information sources will be used:

1. prescribing data in comparison to
2. information received from poison control centers or drug monitoring centers (or other respective sources)

The first source will allow the description of the physician prescribing behavior (including overdose as medication error). This data source will not provide information on intentional overdose of the prescribed dexamfetamine taken by the ADHD patient.

The second source will provide information from the patient/individual perspective and will allow the description of overdose - prescribed or illicit source of dexamfetamine - as the action of patients/individuals. This data source will not reflect physician prescribing behavior.

9. Research methods – drug utilization study

The analysis will include a DUS using databases for Denmark, Finland, Germany, Ireland, Norway, Spain, Sweden, The Netherlands and UK (target countries) to describe the prescription behavior of physicians..

9.1. Study design

This is a multi-country DUS using retrospective data from databases. A single database for all target countries is not available. Therefore, a study approach was chosen which includes multiple data sources to gather drug utilization data for dexamfetamine in European target countries:

- MIDAS Prescribing Insights databases (both international and local databases) will be used for cross-sectional data in Finland, Germany, Ireland, Spain, the Netherlands and the UK.
- National registry data will be used for Denmark, Sweden and Norway.
- For the analysis of the duration of exposure in Germany and the UK, a cohort study using IMS® Disease Analyzer will be performed.

A respective database for Luxembourg is currently not available. Therefore, Luxembourg will be not considered in the DUS.

Information on the selected databases is summarized in section 9.4.

9.2. Setting

Secondary data collected in outpatient setting will be used. The overall observation time will cover the time period from Q3 2015 to Q4 2019. The observation time per country depends on the respective launch date.

Data will be extracted from appropriate databases that are representative for the countries of the study.

All patients in the respective databases in the countries with at least one prescription of dexamfetamine will be included.

9.3. Variables

The following variables will be included in the analysis:

- Patient information:
  - Age
  - Gender
  - Diagnosis associated with the dexamfetamine prescriptions

- Prescribers' medical specialty:
  - In Denmark, Finland, Germany, Norway, Spain, Sweden, The Netherlands
  - GPs only in UK and Ireland

- Derived variables:
  - Average daily dose
  - Percentage of patients with prescribed average daily dose above maximum range

- Additional variables (if available in the database)
  - Co-prescriptions (recorded in the same consultation)
  - New/Switch/Repeat prescriptions, discontinuations
  - Co-diagnosis (recorded in the same consultation)
  - Only IMS® Disease Analyzer data:
    - Duration of exposure (treatment persistence)
    - Dependence syndrome (ICD 10 F15.2) during dexamfetamine or lisdexamfetamine exposure

9.4. Data sources

Overview

The following data sources will be used for the drug utilization study. A more detailed description of the databases is given below.

- Cross-sectional prescription databases
  - IMS MIDAS Prescribing Insights central database
    - Belgium
    - Finland
    - Germany
    - Ireland
    - The Netherlands
    - Spain
    - UK
  - IMS Prescribing Insights local databases (for variables not available in central database)
    - Belgium (Medical Index)
    - Finland
    - The Netherlands (Medical Index)
    - Ireland (Medical Index, if available)
- Longitudinal patient level databases
  - Electronic medical records database
    - IMS® Disease Analyzer (Germany, UK)

- National registries (Denmark, Norway, Sweden)

An overview on variables and database by country is given in Table 2.

Table 2: Data sources and variables of interest by country

Countries \ Variables	Diagnosis	Daily Dose	Age	Gender	Co diagnosis§	Copre-scription	New/ Switch/ Repeat	Treatment Duration	Physician Specialty
Denmark	DK	DK	DK	DK	DK	DK	DK	DK	DK
Finland	PI (I)	PI (I)	PI (L)	PI (L)	PI (L)	PI (L)	PI (L)	-	PI (L)
Germany	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	DA	PI (I)
Ireland	PI (I)	PI (I)	PI (L)§	PI (L) §	PI (L) §	PI (L) §	PI (L) §	-	n/a
Luxem-bourg	-	-	-	-	-	-	-	-	-
Nether-lands	PI (I)	PI (I)	PI (L)	PI (L)	PI (L)	PI (L)	PI (L)	-	PI (L)
Norway	NO	NO	NO	NO	NO	NO	NO	NO	NO
Spain	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	-	PI (I)
Sweden	SW	SW	SW	SW	SW	SW	SW	SW	SW
United Kingdom	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	PI (I)	CPRD	n/a

PI (I): Prescribing Insights (Central Database)
PI (L): Prescribing Insights (Local Database)
CPRD: Clinical Practice Research Datalink
DA: Disease Analyzer
DK: Denmark Local Database (registry)
NO: Norwegian Local Database (registry)
SW: Swedish Local Database (registry)
n/a: not applicable; § on the same prescription; parameter will be analysed in the case the local database is available over the next 5 years)

IMS MIDAS Prescribing Insights

The IMS MIDAS Prescribing Insights database is generated as follows:

IMS regularly collects information from office based GPs and specialists either electronically or by doctor diaries. This methodology gives unique insight into all aspects of the doctor-patient consultation, including diagnosis and prescribing posology (form, strength, frequency).

IMS MIDAS Prescribing Insights information is derived from doctor-patient consultations and the treatment given. The data is collected from a representative sample of doctors practicing in the primary care sector of each country that is monitored. For example, if cardiologists make up 10% of primary care doctors in a country, then 10% of the country's sample will generally be cardiologists. In general, medical data is collected electronically or from diaries that the doctors complete. Each diary gives a full record of consultations over regular sample periods.

The information includes the condition for which a patient is treated and the treatment prescribed. Depending on the country, participating doctors may also be asked to include the age and gender of the patient, and whether this is the patient's first consultation for this condition. All diaries are then sent to IMS for coding. The prescription data collected from the doctor samples is projected upwards to give a total figure for each country (RX). The projection factor is based on the country's methods for collecting data. IMS also adjusts any country-specific data such as corporations and products, to enable accurate international comparisons. European Union countries covered in the central IMS MIDAS Prescribing Insights database are Finland, Germany, Ireland, Spain, the Netherlands and the UK.

In all of these six countries, the central database includes:

- Diagnosis information (using the WHO ICD10 classification)
- Average daily dose

For Germany, Spain and the UK, this central database also includes:

- Age and gender of patients treated
- Co-prescribed products & co-diagnoses (recorded in the same consultation)
- Type of drug (first time, change or repeat)
- Physician specialty (GPs only in UK, who act as gatekeepers)

For the other countries, this information is often available in the Prescribing Insights local databases.

Due to the cross-sectional nature of the database information on treatment duration is not available.

IMS Disease Analyzer for duration of exposure in Germany

The duration of exposure will be analysed using information from the *Disease Analyzer* databases. *Disease Analyzer* (DA) consists of comprehensive observational patient databases from three different European countries (Germany, UK and France). It includes real-life observational patient data collected electronically from more than 3,600 office based physicians in those countries. In total, data from more than 12 million patients are available for analysis.

The physician panel of *Disease Analyzer* in Germany has a mixture of GPs, internists and specialists and contains information on over 7 million patients. For this study, the relevant specialists are paediatricians and psychiatrists/neurologists. It is not possible to track individual patients between different doctors.

Data are transmitted to IMS weekly in Germany, and subjected to a series of quality checks to ensure consistent quality and completeness. Data are available for analysis around 6 weeks after month end. Longitudinal data can be searched for presence or absence of specific events in patients exposed to a drug or diagnosed with a condition and (where relevant) appropriate control groups can be derived.

The *Disease Analyzer* data are collected from various software systems. The software systems are used for administration and/or for billing, which means that it is in the doctors' best interest to use the system fully in order to run their businesses; hence, motivation to record well is high. However, the types of data captured reflect the documentation priorities of the doctors.

Disease Analyzer allows to capture longitudinal information such as disease duration. Information for a specific patient is available for the entire enrolment history of that patient in the database, not only for the annual enrolment period. A detailed definition on how the duration of exposure will be calculated in this DUS will be given in the statistical analysis plan.

Furthermore, using Disease Analyzer, occurrence of a "dependence syndrome" (ICD 10 F15.2) during exposure to dexamfetamine can also be investigated. In contrast to cross-sectional databases, use of Disease Analyzer will allow to capture this diagnosis even if it is made in a separate consultation with the physician participating in the panel.

For this DUS, the following panels will be used:

Germany: 3 panels (GP/internists; paediatricians; psychiatrists/neurologists)

CPRD for duration of exposure in UK

CPRD (Clinical Practice Research Datalink) is one of the world's largest computerised database of anonymised longitudinal medical records from primary care that is linked with other healthcare data. Currently, data are being collected on approximately 5 million active patients from around 639 primary care practices throughout the UK (about (8% of the universe). The CPRD is a well-validated cohort with high-quality information on co-morbidities, therapy and laboratory data, with diagnoses assigned by clinicians.

Further information can be found on the CPRD website: http://www.cprd.com/intro.asp.

CPRD allows capturing longitudinal information such as disease duration. Information for a specific patient is available for the entire enrolment history of that patient in the database, not only for the annual enrolment period. A detailed definition on how the duration of exposure will be calculated in this DUS will be given in the statistical analysis plan.

As for Disease Analyzer, occurrence of a "dependence syndrome" during exposure to dexamfetamine can be investigated.

Information on other databases

Denmark

Data will be collected from the Danish Medicines Agency (DMA) database (*http://dkma.medstat.dk*). The DMA administers legislations on medicinal products, reimbursement, pharmacies, medical devices and euphoriants.

The DMA prepares statistics and analysis on the sales of medicinal products. The data are collected in the Register of Medicinal Products Statistics, which is a database covering total sales of medicinal products in Denmark. The information is collected from Danish community pharmacies, hospital pharmacies, the National Central Laboratory of the Danish Health System (*Statens Serum Institut*) and the Danish Veterinary Laboratory (*Statens Veterinaere Serumlaboratorium*), which registers every dispatch or delivery of medicinal products in Denmark.

The data available in the DMA database are limited. The existing information is limited to patients´ age, gender and daily dose, and is reported by age groups on 5 year intervals. Information about diagnosis (perceived as the indication for the prescription) is not available in the public database.

Norway

The NorPD (Norwegian title: Reseptregisteret; *http://www.norpd.no*) was established on 1st January 2004 at the Norwegian Institute of Public Health. The aim of the NorPD is to collect and process data on drug consumption by humans and animals to map usage in Norway and monitor trends, to be a resource for research in order to see positive and negative effects of drug consumption, to give health authorities a statistical base for quality control of drug use and for steering and planning, and to give prescribers a basis for internal control and quality improvements. The database only monitors drugs that are dispensed by prescription in Norway, and therefore, drugs that are purchased without prescription (OTC drugs) are not included.

The NorPD prescription database (*http://www.lovdata.no/cgi-wift/ldles?doc=/sf/sf/sf-20031017-1246.html#1-1)* contains information from all prescriptions and requisitions that are dispensed at Norwegian pharmacies, both human and veterinary use. NorPD includes the following information to the extent appropriate and necessary to achieve the purpose of the registry: assigned a pseudonym for the patient and the prescriber, patient information (gender, birth year and month of death and month and municipality of residence), prescriber information (gender, year of birth, profession and specialty), drug information including product and package size (part number for both the requested product and dispensed prescribing by generic substitution), the number of packages, delivery group, ATC, and defined daily dose (DDD), reimbursement and refund amounts, price (both for the requested product and dispensed prescribing by generic substitution), dosage and diagnosis code, the pharmacy's license number and the municipality, deliveries to the institution, the health unit registry number (HERE) and local if possible, and the delivery date.

A notification to the ethical committee is required to collect data in Norway.

Sweden

Since 2011 IMS has access to the Swedish Prescribed Drug Register (PDR; 20). This database contains information with unique patient identifiers for all prescriptions dispensed to the whole population of Sweden (9 million inhabitants). For prescribed drugs, the register includes data on dispensed items, substance, brand name, formulation, package size, dispensed amount, dosage,

expenditure, and reimbursement. There is also information on date of prescribing and dispensing, as well as prescriber's profession and practice. All drugs are classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. There is no information on over-the-counter (OTC) medications and for drugs used or administered in hospitals. Further, in order to evaluate the indication, the PDR will be linked to the Swedish patient register (20), which includes ICD-10 diagnosis codes associated with all inpatient and outpatient (specialist) health care contacts, also with national coverage.

A notification to the ethical committee is required to collect data in Sweden.

9.5. Study size

All patients with at least one prescription for dexamfetamine recorded in the databases during the reporting period will be included in the analysis. The exact number of prescriptions/ patent records to be analyzed will depend significantly on the market utilization of dexamfetamine in the target countries.

The sample size formula, based on the normal approximation to the binomial distribution, for calculation of the number of subjects n required to determine a proportion p with a precision e with a two-sided α first-type error is the following:

$$n = \frac{p x (1-p) x z_{1-a/2}^2}{e^2} (1)$$

Based on this sample, and considering a confidence interval of 95%, in order to be able to determine any percentage with a precision of at least ±5%, 384 subjects will be necessary. This corresponds to a hypothetical proportion of 50% which is generally considered as it yields to the largest sample size for each precision level. Respectively, a precision of at least ±10% would necessitate a sample size of 97 dexamfetamine prescriptions cases.

In this study, assuming that we would like to be able to describe any proportion with a precision of at least 10% in each country, a minimum sample size of 100 cases per year is required for any of the countries.

In the case the sample size of 100 cases per single target country is not reached for the annual reports a cumulative analysis of two years data will be considered in the subsequent report.

9.6. Data management

Data will be collected as described in section 9.4.

The study will be conducted according to the standard operating procedures of IMS Health (see section 9.8)

The datasets extracted from the databases will be stored at IMS files to allow analysis in the future. All analysis will be performed using appropriate statistics software (like SAS 9.2).

9.7. Data analysis

General statistical considerations

Descriptive analyses will be performed based on the prescriptions contained in the databases from each reporting period. Extractions will take place once per year for 5 years. The last extraction will include data covering the period from approximately January 2019 to December 2019 The exact data period covered each year will depend on the launch date in each country.

For continuous variables the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be presented. Categorical variables will be displayed with

frequencies and percentages. Confidence intervals will be provided when relevant. Missing values will be reported as missing and no imputation will be conducted.

Results will be provided per country, without statistical comparison between them. Data from different sources will not be directly combined. Study tables will reference the data source used for each set of results.

The details of the specific analysis will be outlined in the statistical analysis plan (SAP). The analysis of this DUS will include the description of patient characteristics (age, gender, indication and co-diagnoses during the same consultation) and prescribing patterns (dosing, specialty).

Exact definitions of all variables (e.g. details on the calculation of average daily dose), the categories of variables to appear in the tables (e.g. age), and subgroup analyses of patients will also be defined in the SAP.

Potential for sampling bias

Overall, some imprecision of estimates may result if the total uptake of dexamfetamine prescriptions in single countries is low. This might be the case especially in the time period immediately after launch and if projected figures are used (please see also "cross-sectional databases" below).

Cross-sectional databases

For the cross-sectional databases (MIDAS Prescribing Insights, Medical Index, National Medical Audit) it is important that the physicians who generally prescribe a product in a country are reflected appropriately in the panel. In this study, pediatricians, neurologists, psychiatrists are expected to be the main prescribers in most countries. In some countries, e.g. UK or Ireland, GPs would also be prescribers, especially for follow-up prescriptions. The prescription data collected from the doctor samples is projected upwards to give a total figure that is nationally representative for each country. However, if the actual prescription number is very low, then imprecision of our estimates will be large which is amplified even more due to the projection.

Longitudinal EMR databases (IMS Disease Analyzer and CPRD)

As the German Disease Analyzer is representative for Germany no major selection bias is expected (18). CPRD in UK covers GPs only. GPs are expected to take care of the follow-up prescriptions for dexamfetamine, whereas the first prescription would most likely be done by a specialist not covered by the database. Therefore, there could be a bias concerning people who only get one prescription from a specialist, but no follow-up prescriptions from the GP. These patients will not be captured. For patients who do get a prescription from a specialist followed by prescriptions from GPs, the start date will not be captured appropriately.

National Registries

No major selection bias is expected for the data obtained from national prescription registries in Nordic countries, because dispatches made at pharmacies nationwide are available.

9.8. Quality control

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IMS Quality Management System (QMS) and in accordance to the following policies and procedures:

POL_QA_001 "Quality Management System" policy

POL_QC_001 "Quality Control Strategy" policy

SOP_QC_002 "Quality Control of Project Deliverables"

According to the policies and procedures above, a Quality Control plan for the study will be developed and executed, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented,
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study

Also, the principal in charge of the study will verify training compliance of IMS employees contributing to the study, as per IMS procedure SOP_QA_007 "Training of Quality and Operational Standards".

The principal in charge of the study is a senior researcher. Qualification, role and responsibilities of the principal in charge of the study are described in OST_OT_014 "Senior Principal RWE- Job Description.

IMS is repeatedly being audited by third parties on their QMS, data, technological infrastructure and services. In case there are findings relevant to the concerned study we will be informed. Next to that MEDICE runs internal and external audits which in this case may be either a documentary or physical audits, and may include, if relevant, assessment of IMS's systems and processes, for example for pharmacovigilance, compliance or data privacy purposes. The decision on whether or not to audit IMS will be taken based on circumstances dictating (for example suspected errors) and could be taken in the frame of broader audit plans for MEDICE's contractors where a risk based approach towards prioritization and selection of contractors is being taken.

9.9. Limitations of the research methods

Panel composition and representativeness

It may be argued that the physicians who participate in panels may have different practice behaviour than other physicians who do not take part in such activity. In PI database, panel members are recruited through stratified random sampling from a universal list of practitioners. Moreover, an annual turnover of 20-30% according to the country in each panel shows a good renewal of doctors.

Data collection

The IMS® Disease Analyzer and CPRD databases have limitations consistent with a provider-sourced EMR database. Patients who seek care outside the EMR practice setting will not have that utilization recorded in the database. However, in UK, GPs function as gate keepers, therefore the majority of information is expected to be available in CPRD. In Germany, parents tend to go with their children to the same pediatrician; therefore information is also expected to be almost complete for children in DA. Nevertheless, it needs to be taken into consideration that Disease Analyzer databases contain prescriptions written by the participating physician, but not actual prescription fills (dispensed drugs).

For calculation of duration of exposure, it needs to be taken into account that any given patient may not be present in the database for the entire duration of his dexamfetamine exposure, so the

apparent duration may be underestimated (for example, if the patient first entered the database when already on the drug; or left the database while being still on the drug).

Furthermore, some patients may receive the dexamfetamine from a source that is not covered, or not completely covered, by the *Disease Analyzer, CPRD or MIDAS prescribing Insights* panels.

Missing information

All information is not available in all databases.

Small sample size, which may be observed especially in the first months after product launch, may result in imprecision of estimates as mentioned in section 9.7. However, sample size numbers are expected to increase within the 5-year study period.

It is not possible to track individual patients between different physicians, any prescriptions that the patient received from a doctor other than the panel doctor will be missing from the analysis. However, if only a few prescriptions are missing, this will not affect the results in the method proposed in this protocol.

9.10. Other aspects

Not applicable.

10. Research methods – data collection on abuse, misuse, overdose, diversion and dependence

Within this drug utilization study it is aimed to provide information on abuse, misuse, overdose, diversion and dependence related to individual dexamfetamine use in Denmark, Germany, Netherlands, Norway and UK.

10.1. Design

The data collection will be performed by active examination of different kind of information sources supplemented by searches in the literature and the internet:

1. Information from poison control centers and drug monitoring centers
2. Information from other sources
3. Identification of information in the literature and the internet

The literature and internet search will be conducted to:

- To identify cases and reports of drug misuse, abuse or overdose, and dependence associated with dexamfetamine in European countries with a specific focus on Denmark, Germany, Norway, The Netherlands and the UK.
- To identify data sources or reporting systems which may contain such information

The review of information sources will be done once per year over the 5-year duration of the DUS. The results will be summarized and provided in the annual DUS report. Before the preparation of the third report the search strategy will be reviewed and modified if necessary (for example new relevant data sources are available).

10.2. Setting

Secondary data collected by different sources as well as information from literature and the internet will be used. The overall observation time will cover the time period from 2012 (launch of dexamfetamine in Germany) to 2018. The observation time per country depends on the respective launch date but will be within the 5 year study period. Table 1 in the protocol depicts the planned

launch dates and the consideration of the country-specific data in the 5 subsequent reports.

10.3. Variables

The data/information will be provided as retrieved from the different sources.

10.4. Sources

Different types of sources will be taken into account to provide information on abuse, misuse, overdose, diversion and dependence.

Poison control centers and drug monitoring centers

The following national drug monitoring centers will be contacted directly to ask for reports associated with dexamfetamine (Table 3). These centers are the National Operational Focal Points for the EMCDDA in Denmark, Germany, The Netherlands, Norway and UK.

Table 3: National Operational Focal Point for the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

Country	Institute	Homepage
Denmark	Danish Health and Medicines Authority	http://sundhedsstyrelsen.dk/
Germany	Deutsche Beobachtungsstelle für Drogen und Drogensucht (DBDD)	http://www.dbdd.de/
Netherlands	TRIMBOS	http://www.trimbos.nl/
Norway	SIRIUS	http://www.sirus.no/
UK	Department of Health	http://www.nwph.net/ukfocalpoint/

Source for national reports:
http://www.emcdda.europa.eu/publications/searchresults?action=list&type=PUBLICATIONS&SERIES_PUB=w203&country=w108

Other sources

In addition, the following sources will be checked for reports on abuse, misuse, overdose, dependence and diversion associated with dexamfetamine in the European target countries Denmark, Germany, Netherlands, Norway and UK.

VigiBase™

VigiBase™, available from Uppsala Monitoring Centre (UMC), is the WHO Global Individual Case Safety Report (ICSR) database (http://www.umc-products.com). A current query for the countries Germany, Ireland, Switzerland and UK with respect to abuse, misuse, overdose, dependence and diversion in December 2013 has provided 7 reports for dexamphetamine over the period of 43 years (1970 to 2013).

EU-ADR

The EU-ADR project is an innovative computerized system to detect adverse drug reactions (ADRs), supplementing spontaneous reporting systems. EU-ADR is a Research and Development project funded by the Information and Communication Technologies (ICT) Area of the European Commission under the VII Framework Program.

Data are available from the Netherlands, UK, Germany and Denmark. The information is from health records.

EudraVigilance

EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA) (http://eudravigilance.ema.europa.eu). EudraVigilance will be available to public after 2016.

For interest will be the EudraVigilance Post-Authorisation Module (EVPM) for post-authorisation individual case safety reports (ICSRs).

Literature and internet

Two types of searches will be conducted:

- Systematic literature research in EMBASE and MEDLINE
- Grey literature research in the www by using Google

An overview on the literature and internet search with respect to search terms and criteria for review is displayed in the annex.

10.5. Study size

Not applicable

10.6. Data management

Not applicable

10.7. Data analysis

Details on the search strategy for the literature databases and other data sources are provided in Annex 4.

Overall, the analysis and the assessment of information will be done separately for:

- information retrieved from published literature and reports (based on aggregated information)
- information obtained from poison control centers and drug monitoring centers or respective sources (based on single reports, if available)

All information on abuse, misuse, overdose, diversion and dependence related to individual dexamfetamine use provided by the single data sources will be summarized and presented in structured tables or in text form. Available data will be provided per country and time period. Data from different sources per country will not be combined. Result tables will reference the data source used for each set of results. The examination of abuse, misuse, diversion and dependency related to individual dexamfetamine use will follow the DUS milestones. Available data and information per country of interest will be provided within the annual DUS reports from 2016 to 2020 considering the country-specific launch date as starting point for data collection and analysis.

Information from the literature and the internet will be also provided per target country.

Information from drug monitoring centers and poison control centers, other databases, literature and internet searches will be summarized per reporting period and compared with the findings from previous reports.

Considering the variety of data sources and structure of reports it is expected that the ability of detailed analyses beyond the structured presentation of findings and the assessment outlined above as well as in Annex 4 is limited. The final analysis approach will be presented in first report.

10.8. Quality control

Reports and information on abuse, misuse, overdose, diversion and dependence retrieved will be reported as received from the different sources. No quality control will be performed.

The following steps are undertaken by IMS to ensure quality and accuracy of presentation of information:

- Methodology review: The search plan and the accompanying extraction table shells will be reviewed and approved by senior staff at the IMS team and at MEDICE. Any changes in the

methodology that the IMS and MEDICE study teams feel are necessary during the course of the study are documented and also reviewed by qualified staff at IMS and MEDICE.

- Statistical review: All tables summarizing the reports per information source and country are reviewed by senior staff at IMS.

10.9. Limitations of the research methods

Availability of reports associated with dexamfetamine

Information on non-medical use is often provided on the substance class and not on a single substance (for example the national reports to the EMCDDA) in European countries. The substance group amphetamines used for the reports includes the following substances: amphetamines (e.g. amphetamine, dextroamphetamine, methamphetamine, methylphenidate).[1] Specific information with respect to dextroamphetamine / dexamphetamine is not provided in the national and the international European reports. In addition, there is no distinction between the origin of amphetamines (drugs for medicinal use or illicit production) with respect to incidence and prevalence of problem drug use. This may limit the informative value of information received from poison control and drug monitoring on potential problem drug use associated with dexamfetamine.

Diversion of a substance is not captured in databases available in European countries at present.

Furthermore, it has to be considered that reports on abuse, misuse, overdose, diversion and dependence at the beginning of the DUS are limited. Whereas dexamfetamine is already on the market in Germany and UK, the number of patients receiving dexamfetamine will be small immediately after launch in the other countries.

Use of different information sources

The use of a wide range of information sources provides the advantage that information is collected comprehensively. It has to be taken also into consideration that the diversity of information may limit the generation of overall conclusions.

10.10. Other aspects

Not applicable.

11. Protection of human subjects

Not applicable.

This study is non-interventional and analysis is based on secondary data use. No identifying data is collected in any of the planned approaches. All databases are set up following local law, including data privacy regulation.

12. Management and reporting of adverse events/adverse reactions

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) good pharmacoepidemiology practice guidelines (19). This is a non-interventional study design which is based on retrospective data collection. This drug utilization study is designed to provide utilization

[1]http://www.emcdda.europa.eu/attachements.cfm/att_65522_EN_Guidelines_Prevalence%20Revision%20280704%20b-1.pdf

data on dexamfetamine, to allow an evaluation of inappropriate use, based on aggregate analyses. Adverse effects are not being measured directly in this study. Therefore, MEDICE will only report aggregate findings as study reports, not individual spontaneous reports.

13. Plans for disseminating and communicating study results

The annual reports will be sent Q4 2016 for 5 years, with a last report Q4 2020 as stated in section 1 "Milestones".

The results of the retrospective database analysis and the information retrieved from drug poison control and drug monitoring centers and other sources as well as the literature review will be provided in the annual report together.

Furthermore, at least one contribution of study findings based on the final report to a scientific conference with focus on public health or medical topics is planned.

Any amendments to the protocol and plans for communication/publication will be made in accordance of the procedures outlined in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance. This study is registered along with study information in the register of PASS maintained by the EMA (ENCEPP/SDPP/7778).

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Annex 1. List of stand-alone documents

none

Annex 2. ENCePP checklist for study protocols

Not applicable

Annex 3. Additional information

none

Annex 4. Literature and internet search

SYSTEMATIC LITERATURE RESEARCH

Criteria for search

The following criteria will be considered for the systematic literature search:

Types of publications:	all
Search terms:	Please refer to the next table
Language of publication:	English, German
Publication status:	Abstracts available
Year of publication:	last 5 years for the first report; for the subsequent years an annual update
	Human

Two electronic databases will be screened: MEDLINE (National Library of Medicine) and EMBASE.

EMBASE: covers the most important journals in the life sciences with a particular focus on comprehensive indexing of adverse drug reactions. All Medline records produces by the National Library of Medicine are included.

MEDLINE/PUBMED: Covers clinical and basic research journals in the life sciences. Employs MeSH terms (subject terms) that allow users to focus their searches.

At the end of search, all the selected articles retrieved from the searches in MEDLINE and EMBASE databases will be examined and those articles cited or included in the reference list of the selected articles and giving relevant information will be considered.

Search terms

Search terms are summarizes in the following table.

Substance and brand	amphetamines, amphetamines, amphetamines, dexamfetamine, dexamphetamine, dextroamphetamine, lisdexamfetamine, lisdexamphetamine, methlyphenidate, Attentin, Dexamed, Dexedrine, other trade names for dexamfetamine, Elvanse, Vyvanse
	substance abuse, substance misuse, substance overdose, diversion, dependence, non-medical use, problem drug use, non-medical drug use
Sources	poison control centers, drug monitoring center
Region and country	Europe, European, Denmark, Germany, Norway, The Netherlands, UK, Scandinavia, Western Europe

The final list of search terms will be provided in the report.

Selection of information

The retrieved publications from the search will be displayed in a way that the author, title, and source information are furnished. The selection of articles for the review will be made by reading the abstracts contents of the publications retrieved and only publications in which abuse, misuse, overdose, problematic drug use, diversion and dependence associated to dexamfetamine are clearly stated and documented will be considered. At the end of search, all the selected articles retrieved from the searches in EMBASE and MEDLINE databases will be examined and those articles cited or included in the reference list of the selected articles and giving interesting information will be considered.

The following selection criteria will be considered for the review of the literature with respect to the

identification of further reporting sources (A) and information / reports on abuse, misuse, overdose, diversion and dependence associated with dexamphetamine (B).

A: Identification of reporting sources

Inclusion criteria	**Exclusion criteria**
European countries, Denmark, Germany, Netherlands, Norway, UK	Centers and databases from outside of EU
Review, surveys, chart review, medical records, monitoring,	
Monitoring centers, databases, poison control centers	
Stimulants	
Abuse, misuse, overdose, diversion and dependence, problem drug use, non-medical drug use, addiction	
	Testing methods

B: Identification of information on abuse, misuse, overdose, diversion and dependence associated with dexamfetamine/lisdexamfetamine

Inclusion criteria	**Exclusion criteria**
European countries, Denmark, Germany, Netherlands, Norway, UK	Reports from outside the EU
Literature review, surveys, interviews, chart review, medical records, monitoring	
Dexamphetamine, dextroamphetamine, Dexamfetamine, dextroamfetamine, lisdexamfetamine, lisdexamphetamine, Attentin, Dexamed, Dexedrine, other trade names for dexamfetamine, Elvanse, Vyvanse	Only information on methylphenidate, only information on stimulants and amphetamine in general
Abuse, misuse, overdose, diversion and dependence, problem drug use, non-medical use, addiction	Reports which only describe use of substances where the use of an authorised medicinal product can be excluded (e.g. different galenic formulations)
	Substance use disorder
	Testing methods

SEARCH IN GREY LITERATURE AND INTERNET VIA GOOGLE

In addition to the systematic literature search web searches will be conducted to identify reports and reporting systems.

Search terms

The following search terms will be used in different combinations. Search terms will be translated to German, Dutch, Norwegian, Danish language.

Search terms:	Abuse, misuse, overdose, dependence, problem drug use, addiction, withdrawal symptoms, substance use disorder, non-medical use, illicit use
	diversion
	Stimulant, amphetamine, dextroamphetamine, dexamphetamine, dextroamfetamine, dexamfetamine, lisdexamphetamine, lisdexamfetamine
	Dexamed, Attentin, Dexedrine, other trade names for dexamfetamine Elvanse, Vyvanse
	Monitoring center/centre, poison control center/centre
	Survey, reporting system, surveillance, information network, interviews, questionnaire
	European, Europe, Denmark, Danish, Germany, German, Norway, Norwegian, Netherlands, Dutch, UK, English, British
Language:	English, German, Dutch, Norwegian, Danish

The complete search strategy will be provided in the annual updates of the reports.

The web search will also include the review of reports and publications from the following sources:

- Reitox Network (http://www.emcdda.europa.eu/about/partners/reitox-network)
- RADARS® System (www.radars.org)
- Phar-Mon / Germany only (www.ift.de)

Reitox Network

REITOX (Réseau Européen d´Information sur les Drogues et les Toxicomanies) is the European information network on drugs and drug addiction. Once per year updates of the national reports published by the national focus points and a European report published by EMCDDA are available.

RADARS® System

The RADARS® (Researched Abuse Diversion and Addiction-Related Surveillance) system was established in US and was acquired by the Rocky Mountain Poison and Drug Center (RMPDC) at Denver Health in 2006.

The aims of the RADARS® system are:

- to measure rates of abuse, misuse and diversion of prescription and illicit drugs
- to identify sentinel events involving the abuse, misuse and diversion of prescription drugs

The RADARS® system is also available in European countries. Please see the table below which presents the RADARS® tools which might be useful to provide data on abuse, misuse, overdose and diversion. As the RADARS® system for European countries is still under development with respect to country coverage MEDICE will follow-up this development with respect to the countries of specific interest (Denmark, Germany, Netherlands, and Norway).

Table 4: RADARS® system in Europe; potential tools with respect to abuse and diversion associated with dexamfetamine

RADARS® Tool	Population	Design/data source	Information provided	Current geographical coverage in Europe*
European Internet Survey (eIS)	Users, youth and adults (focus on college-age)	Self-reported online survey	Demographics, location, experience with prescription drugs and stimulants	UK
Global Toxico-surveillance Network (GTNet)	Young children, adolescents, young adults, adults and elderly	Data collection at poison centers	Spontaneous reports of intentional and unintentional exposure mentions of acute medical events associated with one or more prescription drug of interest	Germany Italy Netherlands Switzerland UK

*might be expanded

Phar-Mon (Germany)

This Germany-specific project reports regularly on the drug use in patients with a history of drug or alcohol dependence. Currently, it is the single monitoring system in Germany for this specific group. The study is repeated annually for a representative sample of patients in outpatient care.