LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dexamfetamin Sea Pharma
(dexamfetamine sulfate)

SE/H/2509/01-03/MR

This module reflects the scientific discussion for the approval of Dexamfetamin Sea Pharma. The procedure was finalised on 2022-09-02. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Dexamfetamin Sea Pharma, 5 mg, 10 mg, 20 mg, Tablet.

The active substance is dexamfetamine sulfate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Dexamfetamin Sea Pharma, 5 mg, 10 mg, 20 mg, Tablet, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Sea Pharma AB applies through the Swedish National Procedure

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
The pharmacological actions of amphetamine and its role in treatment of ADHD has been described in the published scientific literature. It is however unclear to what extent the provided data translates to dexamphetamine. No data or discussion on secondary pharmacology, safety pharmacology or pharmacodynamic interactions were provided. Considering the claimed well-established clinical use of dexamphetamine this is acceptable and further non-clinical pharmacology data is not required.

Pharmacokinetics
The Applicant has presented a review of the scientific published pharmacokinetic data on amphetamine. Most of the presented data is derived from human experience. This is considered acceptable and no further non-clinical pharmacokinetic data is required.

Toxicology
Overall, the toxicity of amphetamine has been sufficiently documented in the published scientific literature.

The in vitro and in vivo genetic toxicity has been reviewed in the submitted scientific literature. The overall conclusion is that amphetamine is not genotoxic.

The carcinogenic potential of d,l-amphetamine sulphate has been studied in F344/N rats and B6C3F1 mice in according to FDA GLP procedures and reviewed in the submitted scientific literature. The study authors concluded that there was no evidence of carcinogenic activity of d,l-amphetamine sulfate in male or female F344/N rats or B6C3F1 mice. It can be concluded that amphetamine is not considered to be carcinogenic at clinical doses.

Reproductive and developmental toxicity of amphetamine has been thoroughly reviewed in the submitted scientific literature. At high doses developmental toxicity was demonstrated in the mouse and the rat.

No data on local tolerance was provided. It is acceptable to evaluate the GI tolerance in the clinic.

The dependence potential of amphetamine is well known and dealt with in the clinic.

The reproductive and developmental toxicity studies showed an increased risk of malformations and reduced litter size at high doses in the mouse and the rat. Peri and postnatal studies in rodents revealed developmental delay, behavioral sensitization as well as increased motor activity in offspring after prenatal exposures to dexamphetamine at dose levels close to human therapeutic dose. The clinical relevance of these findings is unknown. In line with the proposed SmPC wordings the use of dexamphetamine during pregnancy, or when a woman is intendent to become pregnant, is not recommended.

Dexamphetamine was not genotoxic and showed no carcinogenic potential in the reviewed studies, hence the risk of carcinogenicity is negligible.

The proposed wordings in the SmPC sections 4.6 and 5.3 are considered adequate.

Environmental Risk Assessment (ERA)
Dexamfetamin Sea Pharma 5/10/20 mg tablets will be interchangeable with other products containing dexamphetamine sulphate. The introduction onto the market is unlikely to result in any significant increase in environmental exposure to dextroamphetamine sulphate and thus an increased risk to the environment is not expected.

IV. CLINICAL ASPECTS

Pharmacokinetics

No pharmacokinetic studies have been performed with Dexamfetamin Sea Pharma. The Applicant has submitted in vitro dissolution data for Dexamfetamin Sea Pharma demonstrating very rapid dissolution, which is pivotal. In addition, the Applicant has submitted comparative in vitro dissolution data to an approved product that is available on the market (Attentin).

Absorption
Serum peak plasma concentrations are achieved 2-4 hours after dosing.

Distribution
Plasma protein binding is approximately 20 % and the apparent volume of distribution ranges between 4 and 5 L/kg.

Elimination
Dexamfetamine and its metabolites are mainly excreted in the urine. The excretion of amphetamine depends on urinary pH. 48 h after administration of 10 mg dexamfetamine 57% and 7% of the dose was excreted as unchanged parent compound, in acid (pH 4.5 – 5.6) and alkaline (pH 7.1 – 8.0) urine, respectively.

The terminal half-life of dexamfetamine is approximately 8-12 hours in healthy adults. A half-life of approximately 7 hours has been reported in children aged 5-12 years.

The major metabolic pathway is oxidative N-deamination. Deamination produces an inactive metabolite, phenylacetone, which is further oxidized to benzoic acid and then excreted in urine as hippuric acid and glucuronide conjugates. In addition, dexamphetamine is also converted to norephedrine by oxidation and then this metabolite and the parent compound are p-hydroxylated. The enzymes involved in dexamphetamine metabolism have not been clearly defined. CYP2D6 seems to be involved in the formation of 4-hydroxyamphetamine.
Norephedrine and hydroxyamphetamine are pharmacologically active. A small amount of amphetamine is converted to these metabolites.

Interactions
Concomitant use of MAO-inhibitor can cause hypertensive crisis. Dexamfetamine is contraindicated in patients treated with non-selective, irreversible MAO-inhibitor or within 14 days after discontinuing MAO-inhibitor.

Since the CYP enzymes involved in the metabolism of dexamfetamine is not known, concomitant treatment with potent CYP-inhibitors or -inducers should be with caution.

It is not known if dexamfetamine inhibits or induces CYP enzymes in vivo. Concomitant administration with CYP substrates with a narrow therapeutic interval should be with caution.

Urinary acidifying and alkalinizing agents increase respective decrease the urinary excretion of dexamfetamine. Gastrointestinal alkanizing agents increase the absorption of of dexamfetamine, whereas gastrointestinal acidifying agents decrease the absorption of dexamfetamine.

Dexamfetamine has shown to inhibit OCT1 and OCT2 in vitro. The clinical relevance of this interaction is unclear.

Special populations
Limited data is available for most of the special populations. There are no supportive studies on the effect of hepatic or renal impairment on the pharmacokinetics of dexamfetamine. The fraction of amphetamine excreted unchanged in the urine ranges between 7 and 57%, depending on urinary pH. Therefore, the exposure of amphetamine can be prolonged in subjects with hepatic or renal impairment.

Discussion on the pharmacokinetics
This is an application according to Article 10a well-established use. As this is a complete application, the bibliography should cover all aspects of pharmacokinetics needed to make a complete characterisation of the disposition of the compound. For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial.

Oral dexamfetamine IR formulations have been used in the clinical efficacy and safety studies reported in the literature, but it is not known what formulations that were used in the studies. Based on the data provided by the Applicant dexamfetamine cannot be classified as a BCS class I substance (high solubility and high permeability). However, it seems to be a substance in the borderline of BCS class I. BCS class I drugs generally represent a low risk group of compounds in terms of the potential for excipients to affect absorption. BCS class III substances (high solubility with incomplete absorption) could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and in vitro dissolution.

The excipients in Dexamfetamin Sea Pharma are not considered to have an impact on the oral bioavailability of dexamfetamine or on GI motility. The in vitro dissolution experiment indicates very rapid dissolution for Dexamfetamin Sea Pharma (fulfilling dissolution criteria for a BCS class III based biowaiver). Dexamfetamine is not considered to be a substance with a narrow therapeutic index, and the dose is titrated until optimal clinical effect is achieved. Thus, Dexamfetamin Sea Pharma can be expected to behave similarly as the IR formulations used in the literature, considering the high solubility of the active substance, the rapid dissolution of the tablet and the absence of excipients expected to affect bioavailability. The comparison to the approved product Attentin further supports that other IR formulations with dexamfetamin can also be expected to dissolve rapidly.

The basic pharmacokinetic parameters of dexamfetamine have been sufficiently described by the Applicant.

Pharmacodynamics
Amphetamine exists as two stereoisomers that differ in effects. The l-enantiomer (levoamphetamine) produces more cardiovascular and peripheral effects than the d-enantiomer (dextroamphetamine). At low doses, levoamphetamine produces greater arousal than dextroamphetamine, acting primarily on norepinephrine. At higher doses, dextroamphetamine has stimulant properties that are three- to four times as strong as those of levoamphetamine, and acts primarily on dopamine. According to the applicant, few clinical studies of ADHD have documented differences among d-, l- and racemic amphetamine.

The suggested primary action of amphetamine is to increase synaptic concentrations of monoamine neurotransmitters, thereby indirectly enhancing noradrenergic, dopaminergic neurotransmission in the CNS. However amphetamines have complex pharmacological effects that are dose dependent and not fully characterized. Amphetamines substitute for monoamines at the level of the vesicular monoamine transporter (VMAT), disrupting granular storage of monoamine through a reserpine-like effect and increasing cytosolic dopamine. Next, they substitute for monoamines at the level of monoaminergic transporters (notably the dopamine reuptake site [DAT]), and not only inhibit reuptake, but also enter the presynaptic synapse while creating a paradoxal reverse efflux ofmonoamines through the same transporter. Finally, amphetamines can also inhibit the monoamine oxidase (MAO) enzymes at very high doses.

The applicant commented on that it has been suggested that the actions of amphetamine to increase serotonergic drive may have a beneficial effect on anxiety or depression that is often comorbid with ADHD. Thus, enhanced catecholaminergic signalling is the primary mediator of amphetamine's efficacy in ADHD. On the negative side, the same pharmacology is also responsible for amphetamine's major side effects and also its liability for recreational abuse. Therefore, optimising therapeutic efficacy whilst simultaneously maintaining side effects at an acceptable level is a difficult balance requiring careful dose titration in the patient.

Clinical Efficacy and Safety

Background for the WEU procedure

A WEU application is similar to a full application as in article 8.3 with the difference that clinical trial data are replaced by data from published scientific literature of pre-clinical and clinical trials. This published scientific literature should demonstrate that the active substances of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Community for at least 10 years with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I of Directive 2001/83/EC shall apply.

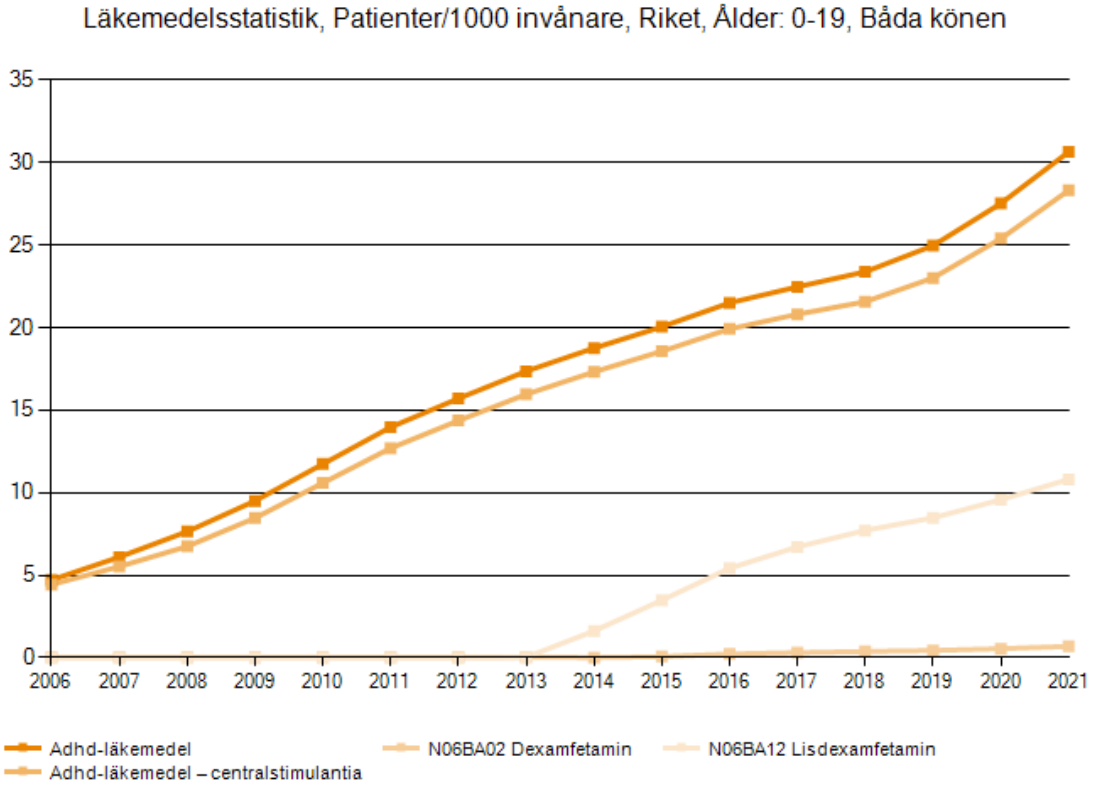
Previous post-marketing exposure
Dexedrine (dexamphetamine, DEX IR) was approved in the UK for pediatric ADHD in 1985. In 2014, Attentin (dexamphetamine, DEX IR) was approved by the RMS UK for pediatric ADHD in a WEU application. The approval in 2014 likely was based on data from previous decades, when therapeutic options for pediatric ADHD largely were limited to short-acting medical products. DEX IR has a long history of use in pediatric ADHD, especially before the marketing of lisdexamphetamine (LDX) approved by EMA in 2013.

In Sweden, according to Läkemedelsregistret at The National Board of Health and Welfare, a minor increase in DEX IR prescription was noted after the pediatric approval in 2014 of Attentin (DEX IR), (37 patients 0-19 years in 2014, 1358 patients 0-19 years in 2020). As off label prescription and adults 18-19 years is included, the numbers treated for pediatric ADHD likely is lower.

Clinical guidelines
One guideline overview article was provided by the Applicant. Before LDX was marketed, several international guidelines recommended various amphetamine formulations including dexamphetamine for pediatric use, of which some were European.

According to current Swedish national guidelines for ADHD in children, adolescents and adults, published by the MPA, methylphenidate is first line treatment for children and adolescents. Atomoxetin could be first line treatment for children in selected cases. LDX or atomoxetine is second line treatment for children and adolescents, whereas guanfacine is a recommended third line pediatric treatment.

The below graph from Läkemedelsregistret at The National Board of Health and Welfare indicates the increasing prescription in Sweden (No. of patients/1000 inhabitants 0-19 years of age) of ADHD medical products, stimulants, LDX and DEX IR respectively. Since 2014, the proportion of pediatric DEX IR use was decreasing as compared to the increasing pediatric use of LDX, all stimulants and all ADHD treatment respectively. Likely this is due to clinically significant differences between products.



From a clinical point of view, a variety of therapeutic options generally is valuable. According to the increasing numbers of patients diagnosed with ADHD, there could still be a need for complementary use of short-acting dexamphetamine (DEX IR) in some pediatric patients.

Taken together, it could be that data provide some support for this WEU application.

Clinical Efficacy

Early studies
The combination of inattentive, hyperactive, and impulsive behaviour in children is recognized as a clinically relevant disorder if these behaviours are severe, developmentally inappropriate, and impaired function at home and in school. This kind of behavioural disorder is described in early literature under a variety of names such as hyperkinesis, hyperkinetic syndrome, minimal brain dysfunction (MBD), attention deficit disorder with hyperactivity (ADDH), or attention deficit disorder (ADD). The existence and sometimes synonymous use of different names for essentially the same symptoms are the consequences of historic development of ADHD research, which began with intensive research of the hyperactivity symptoms, leading to the term “refractory hyperkinetic states”. Only from the 1970s, attention deficits were recognised as core symptoms of the disorder.

Currently, two terms are mainly used synonymously: ADHD and hyperkinetic disorder (HKD). It can therefore be stated as a fact that the term “refractory hyperkinetic states” still exists as an older term describing ADHD. The disorder under the name “ADHD” is now characterized by an inappropriately short attention span as well as age-inappropriate features of hyperactivity and impulsivity.

Literature data on clinical efficacy
In round 2, the Applicant submittted a systematic literature search for clinical efficacy and safety. The studies selected as main and supportive studies for clinical efficacy, respectively were presented in tables for overview.

10 clinical studies on DEX IR were selected as main support of clinical efficacy in children and adolecents (including 2 studies from 5 years age, ie preschool children) of which 6 studies included children up to 12 years age only, ie no adolescents.

In addition, 3 clinical studies on racemic-amphetamine and d- and l-amphetamine were selected as supportive studies of clinical efficacy in children and adolecents, of which 2 studies included children up to 12 years age only, ie no adolescents.

Further, 15 clinical studies on LDX were selected as supportive studies of clinical efficacy in children and adolescents, of which 4 studies included 6-12 years old children only, ie no adolescents, and 1 study on preschool children.

Furthermore, 7 clinical studies on DEX IR in hyperactive children and similar indiactions (including previous definitions of ADHD) were selected as additional supportive studies of clinical efficacy in children and adolecents, of which 4 studies included 6-12 years old children only, ie no adolescents.

In round 3, the Applicant added an updated table with, when available, duration of DEX IR exposure, dosage data, included and completed numbers of subjects per age group 6-12 and 13-17 years, reasons for drop outs and withdrawals, and results with tabulated data for primary and secondary endpoints and functional endpoints. Some original studies were added during 3rd round.

Efficacy short-term

Main studies

In the systematic literature search for clinical efficacy and safey, several studies demonstrated efficacy of DEX IR on the key symptoms inattention, impulsivity an hyperactivity in children, and to some extent in adolescents.

According to main studies, dexamphetamine (DEX IR) exhibited robust short-term efficacy versus placebo on nearly all measures, ie, Conners Parent Rating Scale, and Conners Teacher Rating Scale, Child Behavior Checklist and Teacher's Report Form.

Efficacy was demonstrated in boys with a history of hyperactive, inattentive, and impulsive behaviors interfering with home and school functioning, recruited from schools and health-care providers in the surrounding area. Subjects had to meet the DSM-III criteria for attention deficit disorder with hyperactivity (American Psychiatric Association & Association, 2013) in at least two settings (home, school, or hospital).

Amphetamine was superior to placebo in reducing inattention, hyperactivity, and other disruptive behavior problems. Both dexamphetamine and methylphenidate showed striking clinical efficacy.

Many comorbid subjects had consistent worsening of tics on stimulants, although the majority experienced improvement in ADHD symptoms with acceptable effects on tics. Children's behavior and the mother's well-being, and some aspects of parent-reported and observer-rated family functioning improved, demonstrated by use of well established and validated rating scales and/or questionnaires.

Core symptoms of ADHD and recommended treatments
The main three categories of symptoms of ADHD include inattention, impulsivity an hyperactivity. Recomednations for treatments according to guidelines in EU and US have been brieafly summarised below.

According to the current Swedish national guidelines for ADHD in children, adolescents and adults (Läkemedel vid ADHD – behandlingsrekommendation, published by the MPA), metylphenidate is first line treatment for children, adolescents and adults. Atomoxetin could be first line treatment for children in selected cases. Lisdexamphetamin is second line treatment for adults. Lisdexamfetamin or atomoxetin is second line treatment for children and adolescents, whereas guanfacin is third line treatment. For short acting DEX IR and guanfacine with delayed release, no specific recommendations are available due to limited scientific data. There are concerns regarding DEX IR for the rapid onset of effect in short-acting stimulants., associated with increased risk for abuse, misuse and diversion.

In the US, amphetamine-based stimulants have been first-line treatment options for ADHD with evidence that they demonstrate short-term efficacy versus placebo and long-term effectiveness for the core symptoms of ADHD. Meta-analyses have demonstrated that stimulant and non-stimulant medications for ADHD effectively reduce ADHD symptoms in children and adults, although stimulants may be more efficacious.

Efficacy of dexamfetamine compared to other psychostimulants
Some data demonstrate that most children with ADHD improve significantly on both methylphenidate and methylphenidate and that here was a slight advantage to

methylphenidate on most measures and that the early benefits of stimulants are sustained for at least 6 months.

Overall dexamphetamine and methylphenidate appear comparable in effect, based on studies identified in the systematic literature search as well as in several other published studies. Studies on the relationship between plasma concentration of dexamphetamine and effect in children and in adolescents are very limited and no studies were identified for pre-school children.

Supportive studies
The Applicant has refererred to studies on various other amphethamines.

Studies on lisdexamphetamine
The evidence of efficacy of the prodrug LDX on the three key symptoms of ADHD in children and adolescents is extensive.

Effects on cognition, learning, and academic/school performance
Based on standardized academic achievement measures as well as classroom performance, stimulants improve short-term academic performance and suggest possible long-term benefits in 6-12 years old children. Although academic achievement was not normalized, the medication likely mitigates behavioral and cognitive difficulties, which in turn, impacts academic progress and performance.

Effects on interpersonal and social relationships
Studies including social relationships were limited. However, beneficial effect on behaviors in social and academic settings was demonstrated in 6-12 years old children.

Data to support the posology
There is limited information on DEX IR exposure-response data in children and adolescents. This could be acceptable taking into account the recommendation is to start low (5 mg) and perform individual stepwise dose titration until lowest effective dose is found.
Observed maintenance doses in the main studies were usually in the range 10-20 mg per day for children (6 to <12 years) and 15-20 mg per day in adolescents (>12-17 years). Therefore the recommended maximum dose 20 mg is acceptable.

Treatment for ADHD with comorbidity
Publications on clinically relevant interactions relevant for the comorbidities and co-medications commonly seen in the pediatric ADHD patient population appears to be very limited for DEX IR.

Long-term treatment
Main studies
Long-term data on DEX IR treatment is very limited. A pattern of maintained efficacy in a proportion of patients is seen in the few DEX IR studies. DEX IR is not long-term effective for all children and adolescents with ADHD, and the duration of treatment should not be unlimited. This is clarified in the product information.

Supportive studies
The Applicant has refererred to studies on other amphethamines. Treatment failure rate was considerably lower and time to treatment failure was longer in the racemic amphetamine group in one longer study.

Conclusions on clinical efficacy

The Applicant has presented a review of selected original articles. Some main studies indicate short-term efficacy of DEX IR on the key symptoms inattention, impulsivity an hyperactivity in children. Few adolescents were included in the main studies.

Long-term data on DEX IR treatment is very limited, especially in adolescents. In round 3 the Applicant added a recent 12 months DEX IR study including some support for efficacy in adolescents. Some support is available from long-term studies in other amphetamine formulations. Between studies, overall a pattern of maintained efficacy in a proportion of patients is noted. Clinical data related to age, gender or subtype of ADHD are sparse. Some data might indicate age and gender differences, with potential impact on dosage.

It is considered that based on relevant published literature, the applicant has provided acceptable justifications for efficacy regarding a pediatric ADHD indication in the present WEU procedure.

Clinical safety

Literature data on clinical safety
In round 2 the Applicant had performed a new systematic literature search on clinical efficacy and safety of DEX IR treatment in ADHD in children and adolescents. An overview of clinical studies to support exposure and safety was presented. The studies referred to were generally small, short randomized, double-blind and placebo controlled and/or cross over studies in children and adolescents with ADHD.

It was noted there is limited safety data from long-term pediatric use of DEX IR, in particular per age group (pre-school, children and adolescents).

Discussion of safety and tolerability
Well known common adverse events of DEX IR such as headache, insomnia and loss of appetite were reported in the publications above.

Other adverse events of DEX IR and other stimulants include heart palpitations, tachycardia, elevated blood pressure, over-stimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, exacerbation of motor and phonic tics and Tourette disorder, headache, dry mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances, constipation, anorexia, weight loss, urticaria, impotence, and changes in libido.

Side effects of amphetamines include peripheral release of norepinephrine, resulting in cardiac stimulation and vasoconstriction. Increased heart rate and blood pressure, palpitations, and sweating are common. Increased anxiety can occur in predisposed patients. Mood may be temporarily enhanced, but the effect is generally not sustainable alone in patients with depression.

At a high dose, an amphetamine may precipitate psychosis, although most typically delusions are of the persecution subtype and are reversible with cessation of the medication. As with all psychotropic medications, however, more severe and irreversible psychiatric complications can emerge.

Early amphetamine treatment has been linked to slowing in height and weight growth in some children. Because the number of prescriptions for amphetamines has increased several-fold over the past decade, an amphetamine-containing formulation is the most commonly prescribed stimulant in North America.

Amphetamines are the most abused prescription medications. Although early treatment does not increase risk for substance abuse, few studies have tracked the compliance and usage profiles of individuals who began amphetamine treatment as adults. Overall, there is concern about risk for slowed growth in young patients who are dosed continuously, and for substance abuse in patients first medicated in late adolescence or adulthood.

A few studies have compared the types and rates of adverse events associated with administration of e.g clonidine, amphetamine and methylphenidate to children with ADHD. In general, these studies found similar side effect profiles for the two drugs. One of the larger and best controlled studies noted that the severity of adverse events may be greater for amphetamine, especially with respect to insomnia, negative affect, irritability, proneness to crying, anxiety, sadness/unhappiness, and nightmares.

Data for DEX IR effects on sleep latency and sleep quality in children and adolescents was not found.

Cumulative exposure data
In round 3, the Applicant added tabulated cumulative subject numbers per study for DEX IR treatment of ADHD in children 6-12 years and in adolescents 13-18 years respectively, from publicly available studies and some unpublished studies.

In the public data identified, in total 1 599 children and adolescents were exposed to DEX IR including only 78 in pure adolescent age groups, 540 in pre-pubertal children and adolescents combined age groups (including 379 pediatric patients in a retrospective study, and 981 in pre-pubertal children age groups (including 555 patients in a retrospective study).

Adverse events associated with DEX IR versus MPH appear similar at the group level but may differ substantially in individual children. Overall, insomnia and decreased appetite were significantly associated with stimulants. No treatment effect on emotional symptoms was detected. Most of the children experienced no or modest adverse events.

Analysis and discussion
Adverse events associated with DEX IR versus MPH appear similar at the group level but may differ substantially in individual children. Overall, insomnia and decreased appetite were significantly associated with stimulants. No treatment effect on emotional symptoms was detected. Most of the children experienced no or modest adverse events. In some studies the following side effects were more severe on DEX IR than MPH: insomnia, irritability, proneness to crying, anxiousness, sadness/unhappiness, and nightmares.

Insomnia is more frequently reported as an ADR for stimulants in comparison to placebo, and slightly more frequently reported for DEX IR compared to MPH in pre-pubertal children and adolescents assessed on a group level. Due to the limited data for DEX IR in adolescents, additional data for safety is available by LDX studies, showing higher frequencies of decreased appetite, weight decrease and insomnia for LDX, compared to placebo.

Overall the ADRs identified are well known and were generally mild or moderate and transient, and DEX IR is generally considered well tolerated in both the paediatric population

and adolescents. Appetite decrease and insomnia are the ADRs that most often demonstrates a statistically significant difference for DEX IR vs placebo or baseline.

The ADRs and frequencies identified from the studies specified are in line with the product information.

Interactions with co-medications in common co-morbidities
The Applicant considers that most of the PD interactions with comedications given in the SmPC section 4.5 are justified based on the Primary action of DEX IR, i.e., by the increased levels of synaptic concentration of monoamine neurotransmitters (dopamine, noradrenaline and serotonin) by inhibiting reuptake, by releasing dopamine and noradrenaline from dopaminergic neurons, and, at very high doses, inhibiting monoamine oxidase. Similarly, DEX IR as a victim drug, any comedication that can affect the levels of these neurotransmitters could decrease or increase the pharmacologic effect of DEX IR.

Even though amphetamines are extensively studied, still the mechanism of action is not fully understood. ADHD in children and adolescents is one of the psychiatric diseases with the most frequent comorbidities (60 – 80%) and the comorbidities commonly observed are e.g., autism, tic disorder, depression, anxiety, ODD and conduct disorder (CD). In the following paragraphs relevant concomitant medications are discussed.

Co-medications in comorbidity disorders with ADHD
Depression is treated with antidepressants such as selective serotonin reuptake inhibitors (SSRI), Serotonin and norepinephrine reuptake inhibitors (SNRIs), those with a dopamine profile and Monoamine oxidase inhibitors (MAOIs).

MAO-inhibitors and amphetamines used concomitantly may increase risk for cardiovascular adverse effects (hypertension, tachycardia, dysrhythmias) particularly because of overstimulation of the adrenergic receptors and co-treatment may provoke synergistic monoaminergic effects. The combination is contraindicated and amphetamine should not be administered during or within 14 days following the administration of MAOIs.

Due to synergistic effects on noradrenergic neurotransmission, concomitant use of tricyclic antidepressants and amphetamines may lead to hypertension and tachycardia, cardiac arrhythmias, or increased CNS stimulation. Clinical data is limited but adverse cardiovascular effects have been reported in use of sympathomimetics and tricyclic antidepressants**.**

In adult patients, co-administration of SSRIs or SNRIs with stimulants in ADHD with comorbid anxiety or depressive symptoms was studied. DEX in combination with SSRI/SNRI therapy appear beneficial in adult ADHD patients with comorbid anxiety or depression. It could be that treatments of depression and anxiety need to include the targeting of the ADHD symptoms in order to achieve better resolution of anxiety symptoms.

Some data suggest that both lithium and valproate can attenuate DEX IR-induced changes in brain activity in a task dependent and regionspecific manner, conceivably via similar effects on phosphoinositol second messenger system (PI-cycle) activity.

For antihistamines there is a theoretical risk with simultaneous administration like hydroxyzine due to the potential monoamine oxidase inhibition caused by dexamphetamine.

Coadministration of guanfacine and MPH or amphetamines was generally safe and associated with statistically significant and clinically meaningful ADHD symptom improvement in children and adolescents with suboptimal response to a psychostimulant alone.

Regarding uncommon or rare severe psychological or behavioral reactions to stimulants, controlled studies have not been large enough to pinpoint risk factors or determine differential risk by treatment assignment. A common observation across studies of the pharmacokinetics, pharmacodynamics, and safety profiles of amphetamine is the high degree of inter-individual variability across most measures and endpoints.

Overall, the safety profile of DEX IR in pediatric use is considered well known. During earlier decades of pediatric use e. g. in the UK, the safety profile of DEX IR has been considered acceptable. The ADRs identified in the studies of DEX IR in pediatric ADHD appears to be generally mild or moderate and transient. Among the common unfavourable DEX IR effects are headache, insomnia and loss of appetite. Other unfavourable effects include cardiovascular risk, growth and appetite suppression, pubertal development suppression, psychotic symptoms, sleep disturbance, suicide, tics and misuse, abuse and diversion.

Robust data on the long-term safety of pediatric treatment with DEX IR with ADHD is limited, in particular in adolescents. Some additional data is available from other amphetamine formulations. Studies indicate that especially DEX IR may have a higher abuse potential than LDX. The product is not intended for use in adults. In the product information is also included that special caution should be taken in treatment of adolescents with DEX IR, and that usually the treatment is ended during or after puberty.

Overall it is considered that based on relevant published literature, the applicant has provided acceptable justifications for acceptable safety in pediatric treatment of ADHD in this WEU procedure.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

Risk Management Plan

The MAH has submitted a risk management plan (Version 0.1, final sign off 7 February 2019), 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 Dexamfetamin Sea Pharma.

Safety specification

Module SVIII - Summary of the safety concerns
Important identified risks
1. Drug abuse and dependency
2. Misuse and diversion
3. Cardiac and cardiovascular disorders, including increased blood pressure versus hypertension and increased heart rate, tachycardia, arrhythmias
4. Cardiomyopathy
5. Increased risk of depression

6. Increased risk of aggressive / hostile behavior
7. Psychotic reactions, e.g. hallucination (visual, auditory, skin sensation), and mania
8. Withdrawal syndrome
9. Decreased rate of growth and development / anorexia
10. Serious skin reaction

Important potential risks
1. Ischaemic / serious cardiovascular events, e.g. myocardial infarction, sudden death, cyanosis, QT prolongation
2. Cerebrovascular disorders, e.g. stroke (ischaemic and haemorrhagic)
3. Migraine
4. Raynaud's syndrome
5. Suicidal ideation
6. Tics / Tourette's / dystonias
7. Repetitive behaviours
8. Seizures
9. Delayed sexual maturation and neonatal growth
10. Neonatal toxicity, e.g. cardio-respiratory toxicity
11. Carcinogenicity
12. Overdose
13. Off-label use

Missing information
1. Long-term safety (cardiovascular, growth, neurological, cognition and psychotic)
2. Pregnancy
3. Patients with renal and hepatic insufficiency
4. Treatment in children under 6 years, adults, and elderly

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and additional pharmacovigilance activities below are proposed.

Risk minimisation measures

Important identified risks

Safety concerns	Additional Pharmacovigilance	Additional Risk Minimisation
drug abuse and dependency	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) letter to pharmacists, parents and carers specific questionnaire
misuse and diversion	SmPCs: section 4.4 prescription only medicine	educational tool (physician's guide to prescribing and checklists) letter to pharmacists, parents and carers specific questionnaire
cardiac and cardiovascular disorders, including increased blood pressure versus hypertension and increased heart rate, tachycardia, arrhythmias	SmPCs: section 4.3, section 4.4, section 4.5, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists)
cardiomyopathy	SmPCs: section 4.3, section 4.4, section 4.5, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists)
increased risk of depression	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists)
increased risk of aggressive / hostile behaviour	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
psychotic reactions, e.g. hallucination (visual, auditory, skin sensation), and mania	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
withdrawal syndrome	SmPCs: section 4.4, section 4.8 prescription only medicine	none proposed

decreased rate of growth and development / anorexia	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
serious skin reaction	SmPCs: section 4.8 prescription only medicine	none proposed

Important potential risks

ischaemic / serious cardiovascular events, e.g. myocardial infarction, sudden death, cyanosis, QT prolongation	SmPCs: section 4.3, section 4.4, section 4.5, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
cerebrovascular disorders, e.g. stroke (ischaemic and haemorrhagic)	SmPCs: section 4.3, section 4.4, section 4.5, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
migraine	SmPCs: section 4.4, section 4.8 prescription only medicine	none proposed
Raynaud's syndrome	presciption only medicine	none proposed
suicidal ideation	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
tics / Tourette's / dystonias	SmPCs: section 4.3, section 4.4, section 4.8 prescription only medicine	educational tool (physician's guide to prescribing and checklists) specific questionnaire
repetitive behaviours	SmPCs: section 4.4, section 4.8 prescription only medicine	none proposed
seizures	SmPCs: section 4.4 prescription only medicine	none proposed
delayed sexual maturation and neonatal growth	SmPCs: section 4.6, section 5.3 prescription only medicine	none proposed

neonatal toxicity, e.g. cardio-respiratory toxicity	SmPCs: section 4.6, section 5.3 prescription only medicine	none proposed
carcinogenicity	SmPCs: section 5.3 prescription only medicine	none proposed
overdose	SmPCs: section 4.1, section 4.2, section 4.9 prescription only medicine	educational tool (physician's guide to prescribing and checklists)
off-label use	SmPCs: section 4.1, section 4.2 prescription only medicine	educational tool (physician's guide to prescribing and checklists) letter to pharmacists, parents and carers specific questionnaire

Missing information

long-term safety (cardiovascular, grwoth, neurological, cognition and psychotic)	SmPCs: section 4.4 prescription only medicine	educational tool (physician's guide to prescribing and checklists for ongoing monitoring)
pregnancy	SmPCs: section 4.6 prescription only medicine	none proposed
patients with renal and hepatic insufficiency	SmPCs: section 4.2, section 4.4 prescription only medicine	none proposed
treatment in children under 6 years, adults, and elderly	SmPCs: section 4.1, section 4.2	none proposed

Summary of the RMP
The submitted Risk Management Plan, Version 0.1, final sign off 7 February 2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
At the request of the MPA;
Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Attentin 5 mg tablets, UK/H/5007/001/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality
All the outstanding quality issues have been satisfactorily resolved and approval of the application can be accepted from a quality point of view.

Pharmacokinetics
All the pharmacokinetic issues have been satisfactorily resolved. The Applicant has established a sufficient bridge between the dexamfetamine IR formulations used to support clinical efficacy/safety and their own formulation. The application can be recommended for approval from a pharmacokinetic point of view.

Clinical efficacy and safety
Publicly available studies selected by the Applicant are considered to indicate short-term efficacy of immediate-acting dexamphetamine (DEX IR) in pediatric treatment of ADHD, on the key symptoms inattention, impulsivity and hyperactivity. Rather few adolescents were included in the studies. Long-term data on DEX IR pediatric treatment is very limited especially in adolescents. There is one recent 12 months DEX IR study providing some support for maintained efficacy in adolescents.
Clinical data related to age, gender or subtype of ADHD are sparse. Some data might indicate age and gender differences, with potential impact on dosage. Taking into account that dosage is individually titrated, no such information has been included in the SmPC 4.2. The Applicant is encouraged to update the SmPC on this point whenever justified by data.
Between studies, a pattern of maintained efficacy in a proportion of patients is noted. Some support is available from earlier pediatric long-term studies in other amphetamine formulations, such as racemic amphetamine in IR formulation.
Overall it is considered that based on relevant published literature, the applicant has provided acceptable justifications for the favourable effects regarding a pediatric ADHD indication in the present WEU procedure.

The safety profile of DEX IR in pediatric use is well known. It appears that during earlier decades of pediatric use e. g. in the UK, the safety profile of DEX IR was considered acceptable. Overall the common ADRs identified in the Applicant’s selection of studies on DEX IR in treatment of pediatric ADHD are generally mild or moderate and transient. Among the common unfavourable DEX IR effects are headache, insomnia and loss of appetite. Other unfavourable effects include growth and appetite suppression, pubertal development suppression, psychotic symptoms, sleep disturbance, suicide, tics and misuse, abuse and diversion, and cardiovascular risk..

Robust data on the long-term safety of pediatric treatment with DEX IR with ADHD is limited, in particular in adolescents. Some additional data is available from other amphetamine formulations, e.g. racemic amphetamine in IR formulation.
Some studies indicate that especially DEX IR formulations may have a higher abuse potential than e.g. lisdexamphetamine. It is included in the SmPC 4.4 that treatment with DEX IR is usually stopped in puberty or thereafter, and in SmPC 4.1 and 4.2 that the product is not approved for use in adults. It has been clarified in 4.4 that special caution should be taken in treatment of adolescents with DEX IR.
Overall it is considered that based on relevant published literature, the applicant has provided acceptable justifications for acceptable safety in pediatric treatment of ADHD in this WEU procedure.

In summary it is considered that based on relevant data, the favourable and unfavourable effects of dexamphetamine IR in the treatment of pediatric ADHD have been established. All the outstanding issues have been satisfactorily resolved in this procedure. The application can be accepted for approval from a clinical point of view provided that routine risk communication: information and warnings in several sections of the SmPC and PL as we as additional risk minimization measures as described in Section VII.3 are implemented.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for adverse events, abuse/dependence/misuse/diversion, and pregnancy.

Risk minimisation measures
Routine risk communication: information and warnings in several sections of the SmPC and PL, pending of which risk (ie SmPC section 4.1, SmPC section 4.3, SmPC section 4.2, SmPC section 4.4, SmPC section 4.5, SmPC section 4.6, SmPC section 4.8, SmPC section 4.9, SmPC section 5.3, PL section 1, 2, 3, 4).

Legal status: Prescription only medicine. Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders.

Additional risk minimisation measures including educational material
The potential for abuse and misuse and related complications are known and appropriate warnings are in the SmPC and PIL for the DEX product of Sea Pharma. To avoid/reduce abuse/misuse and associated events, Sea Pharma will develop educational material for treating physicians, pharmacists, and carers. The products of Sea Pharma are only claimed to be authorised for children and adolescents.

VII. APPROVAL

Dexamfetamin Sea Pharma, 5 mg, 10 mg, 20 mg, Tablet was approved in the national procedure on 2022-09-07.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	No	N/A	N/A	Update of the previously published version of the PAR (section IV and section VI).
SE/H/2509/01-03/MR	N/A	Yes	2024-05-22	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)