COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Adhesa 5 mg tablets (dexamphetamine sulphate)

NL/H/6293/001/MR

Date: 15 June 2026

This module reflects the scientific discussion for the approval of Adhesa 5 mg tablets. The procedure was finalised on 13 August 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
F_{PEN}	Market penetration factor
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PEC_{sw}	Predicted environmental concentration in surface water
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Adhesa 5 mg tablets, from ACE Pharmaceuticals B.V.

The product is indicated as part of a comprehensive treatment program for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. A comprehensive treatment program typically includes psychological, educational and social measures.

Diagnosis should be made according to DSM-5 criteria or the guidelines in ICD-10 and should be based on a multidisciplinary comprehensive evaluation of the patient.

Dexamfetamine is not indicated in all children with ADHD and the decision to use dexamfetamine must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion.

Treatment should be under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, which concerns a well-established use (WEU) application.

This mutual recognition procedure concerns a bibliographical application based on well-established medicinal use of dexamphetamine sulphate. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Dexamphetamine sulphate was first introduced into the European market at least ten years ago for the treatment of ADHD in children and adolescents and has a recognised efficacy and an acceptable level of safety. The MAH submitted a justification for bridging between their product and the products used in the literature. Based on the comparable composition of the pharmaceutical form and excipients of the current product and those mentioned in literature, it is expected that the exposures with the current formulation and with the formulations in the literature are comparable. The documentation submitted by the MAH covers all aspects of the safety and/or efficacy assessment and includes and refers to (reviews of) the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and comparative epidemiological studies.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Finland, Germany, Norway and Sweden.

General comments on the application

The marketing authorisation for this product was initially requested via a decentral procedure (NL/H/5396/001/DC) based on Article 10a of Directive 2001/83/EC, which was finalised with a negative outcome as it was considered that appropriate bridging was not established between the new product and the products described in the used literature. Following a successful objection procedure to this decision, a national authorisation was granted (RVG 128087) on 27 July 2023, which forms the basis for the current mutual recognition procedure NL/H/6293/001/MR. See section 'VI. Overall conclusion' for more information.

II. QUALITY ASPECTS

II.1 Introduction

Adhesa is a white to off-white, round flat, bevelled edge tablet with a half score line (bisect break line) on one side. The score line is only intended to facilitate breaking for easier swallowing, and not to divide it into equal doses. Each tablet contains 5 mg of dexamphetamine sulphate, corresponding to 3.7 mg dexamfetamine as active substance.

The excipients are: isomalt (E953), crospovidone (E1202) and magnesium stearate (E470b).

The tablets are packed in transparent polyvinylidene dichloride/polyethene/ polyvinyl chloride/aluminium (PVdC-PE-PVC/Al) blisters in a carton box or in a plastic child-resistant high-density polyethylene (HDPE) container with polypropylene (PP) closure in a carton box.

II.2 Drug Substance

The active substance is dexamphetamine sulphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder, freely soluble in water, very slightly soluble in ethanol 96%, practically insoluble in methylene chloride. Dexamphetamine sulphate contains one chiral centre and shows isomerism, for this product the S-enantiomer is consistently produced, optical rotation is controlled by the active substance manufacturer. No indication of polymorphism of dexamphetamine sulphate was found in the literature of the Ph.Eur. monograph 2752. This has been supported by a characterisation study performed by the manufacturer, no shifts in infrared adsorptions due to different polymorphic forms or amorphous material were observed in the three validation batches and reference material. Therefore it is concluded that dexamfetamine sulfate shows no polymorphism. Test for particle size distribution of the dexamfetamine sulfate is included by manufacturer in the release specification and during the retest period.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for

pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted. Therefore, no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements of the CEP for particle size distribution. An acceptable justification is provided for not including a test for microbial quality in the drug substance specifications. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

As no retest period is stated on the CEP, results of stability studies of the drug substance are provided, which sustain the retest period for the drug substance of 48 months when stored under the stated conditions. This is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The choice of excipients is based on the composition of the similar product Amfexa, authorised in de EU. No compatibility studies of drug substance with the chosen excipients have been performed. However, this is acceptable based on the long marketing experience of other dexamphetamine products authorised in de EU, which have the same qualitative composition. No formulation development studies have been presented but based on the above and the standard quantities of excipients used, this is acceptable. To support the bridging of this product to the products described in the literature, the MAH performed different *in vitro* studies as described in section IV (Bridging to the products described in the literature). For this, comparison of dissolution profiles have been performed with one batch of the proposed product and Amfexa, Dexamphetamine sulfate capsules and Attentin, in four media throughout physiological pH. In all cases, for all products, very rapid (>85% in 15 minutes) dissolution is observed. Therefore it can be concluded that the products have similar dissolution profiles. Development of the dissolution test method has been sufficiently described. The discriminatory power of the method has not been fully demonstrated, however this is accepted based on the very high solubility of the drug substance. Overall, the development of the manufacturing process has been sufficiently described and its considered acceptable.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. Flow chart, description of manufacturing process and critical process parameters are provided and include sufficient details. In-process controls and intermediates are described. The holding times are described in the dossier. The main steps of the manufacturing process are pre-mixing, mixing, sieving, lubrication and compression of the final mixture into tablets. Process validation data on the product have been presented for three full batches in accordance with the relevant European guidelines. All results meet the specification limits, except the results of the breakability tests performed with the first validation batches. Based on the results of additional tests after changing the tablet shape and resistance to crushing, a flat bevelled edge shape has been chosen to improve the breakability and to comply with the Ph. Eur. requirements. Batches with this shape and resistance to crushing will be manufactured and post authorisation. The approach is acceptable, however breakability of drug product into equal doses is not considered demonstrated, the required warnings are therefore included in the SmPC.

Control of excipients

The excipients comply with the Ph.Eur. requirements with additional tests for some excipients, which has been adequately justified. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, average mass, dimensions, resistance to crushing, disintegration, dissolution, degradation products, assay, uniformity of dosage units (content uniformity), water activity, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Release and shelf-life specifications are identical except for the limit for total impurities, which are higher at end of shelf life. The drug product specifications are acceptable.

A risk assessment on elemental impurities performed in line with ICH Q3D Option 2b, has been submitted. No risk was identified. It is agreed that no additional control for elemental impurities is needed at release. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. The conclusion that no additional control on nitrosamines is necessary is endorsed.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three batches from the proposed production site(s) have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three validation scale batches stored at 25°C/ 60% RH (up to 39 months), 30°C / 65% RH (up to 14 months) and 40°C/75% RH (6 months). The batches were stored in the two proposed packaging (PVdC-PE-PVC/Al blister or HDPE container with PP closure). The stability was tested in accordance with applicable European guidelines. Supportive data on two laboratory scale batches with a different tablet

shape than the commercial batches (up to 24 months) have been submitted. The results on laboratory batches are considered as supportive data only.

In-use stability data have been provided for the HDPE container stored at 25°C/ 60% RH and simulating the conditions as used by the patient. Results demonstrated that the product remains stable for 3 months following first opening of the container and when stored below 25°C. The stability was tested in accordance with applicable European guidelines. Microbial quality has been tested at start and end of the stability studies. Instead of photostability studies, forced degradation studies of the drug substance in several conditions (including UV-light) were performed according to the ICH Q1B. The results demonstrate that the drug substance and mixes of the drug substance and excipients of the product are not sensitive to light. This is acceptable.

On basis of the stability data submitted, the following shelf life with labelled storage conditions was granted:

- Blister: 3 years, when stored below 25°C.
- Container: 2 years, when stored below 25°C. After first opening: 3 months.

Special precautions for storage: store below 25 25°C.

The long-term stability studies on production batches do not yet cover the maximum shelf life period expected. As requested, the MAH commits to continue this stability programme up to 60 months for blister and containers according to the protocol submitted. Furthermore, at several time points later than the claimed shelf life and in both proposed packaging, unknown impurities above the identification threshold relevant for the maximal daily dose of 40 mg have been observed. The MAH committed to identify and quantify these impurities and introduce as specified impurities in the drug product specification. This will be performed before extension of the shelf life and will be requested via a regulatory variation.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. A certificate from the supplier has been submitted for magnesium stearate demonstrating that it is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Adhesa has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- To submit the validation report of the particle size distribution method via a variation as soon as possible.

III. NON-CLINICAL ASPECTS

The submitted literature data are adequate to assess the non-clinical aspects of dexamphetamine sulphate for the purpose of a well-established use application. An overview on the submitted literature and main conclusions is given below.

III.1 Pharmacology

Amphetamine is a compound that was discovered in 1887 and has been used for a variety of conditions very freely until it became a highly restricted Controlled Drug with restricted indications. It was first introduced onto the market in 1935 as a treatment for narcolepsy (for which it is still used today), mild depression, post-encephalitic Parkinsonism and a raft of other disorders. Dexamphetamine is a central nervous system (CNS) stimulant and an amphetamine enantiomer. The amphetamine molecule exists as two enantiomers, levoamphetamine (left handed) and dextroamphetamine or dexamphetamine (right-handed). Dexamphetamine exhibits more pronounced effects on the CNS than levoamphetamine (Heal et al., 2013).
Adhesa 5 mg tablets contains dexamphetamine sulphate and has been developed for the treatment of attention deficit hyperactivity disorder in children and adolescents who are ineffectively treated with methylphenidate.

ADHD may be the result of insufficient production of norepinephrine and dopamine in the prefrontal cortex (Dickstein et al., 2006). As such, the executive functions carried out by the prefrontal cortex are impaired, resulting in forgetfulness, distractibility, impulsivity, and inappropriate social behaviours. Amphetamine acts on adrenergic and serotoninergic synapses. It increases dopamine release, thereby inducing wake-promotion. Amphetamines are non-catecholamines, sympathomimetic amines with CNS stimulant activity. Amphetamines are thought to both promote marked neurotransmitter release into the synaptic cleft as well as disrupt normal reuptake of neurotransmitters, thereby increasing levels of norepinephrine and dopamine in these regions of the brain and affecting executive functioning. They also block norepinephrine and dopamine reuptake into the presynaptic neuron by competitive inhibition. Released norepinephrine affects both alpha-adrenergic receptor sites and beta-adrenergic receptor sites (DrugBank, 2021; Heal et al., 2013; Mignot, 2012; Punja et al., 2016).

Available literature on ADHD-like animal models suggest that dexamphetamine affects behaviour in these animals. In Coloboma mice that display spontaneous hyperactivity, treatment with dexamphetamine reduced hyperactivity (Bruno et al., 2007; Wilson, 2000). Mice that lack functional substance preferring, tachykinin-1 receptors (NK1R), either through drug antagonism or gene ablation, display hyperactivity that was prevented by psychostimulants (D-amphetamine or methylphenidate) (Yan et al., 2009).

Dexamphetamine has a stimulatory effect on brain functions. At high doses, neurotoxicity may occur, however, this is not observed following chronic administration of low doses (as intended for the current indication) (Berman et al., 2009).

In addition, amphetamines can induce peripheral release of norepinephrine, resulting in small increases in heart rate and blood pressure, palpitations, and sweating (Hennissen et al., 2017; Mignot, 2012; Zukkoor, 2015).
From two studies, it is concluded that that the long-established clinical practice of the use of stimulant medication to treat young children with ADHD does not affect the risk for substance abuse in adulthood (Volkow & Swanson, 2008).
In the CHMP-referral on dexamphetamine, it was concluded that the benefit/risk ratio of dexamphetamine is favourable when used as second line treatment of ADHD and that risk minimisation measures are appropriate to mitigate the risks of misuse and diversion.

III.2 Pharmacokinetics

Due to its lipophilic nature, dexamphetamine is rapidly and well absorbed (>90%) after oral administration (Markowitz & Patrick, 2017).
Protein binding of amphetamines is low (16-20%) (Quinn et al., 1997). Amphetamine is widely distributed throughout the body and readily penetrates the central nervous system (Markowitz & Patrick, 2017). Concerning the distribution of the two amphetamine isomers, it has been shown that protein binding and distribution volumes of (S)-(+)- and (R)- (–) amphetamine enantiomers are similar (Wan et al., 1978), whereas the elimination half-life of (S)-(+)-amphetamine was shorter than that of the (R)-(–)-isomer because of the faster metabolism of the more pharmacologically active enantiomer (Angrist et al., 1987; Wan et al., 1978). The volume of distribution of methamphetamine appeared to be similar to that of amphetamine and unaffected by the route or time of administration (Shappell et al., 1996). Amphetamine is highly metabolised. The pharmacologically active metabolite 4-hydroxyamphetamine is formed via aromatic hydroxylation (catalysed by CYP2D6) (Markowitz & Patrick, 2017). Additionally, b-hydroxylation occurs and is stereoselective for d-amphetamine to form norephedrine, which is also pharmacologically active. Amphetamine is also oxidised to phenylacetone via oxidative deamination (Dring et al., 1970).

Dexamphetamine is eliminated through the kidneys and is dependent on pH and urinary flow rates. Excretion is more rapid at lower pH (Beckett et al., 1965 a, b; Beckett et al., 1969; Markowitz & Patrick, 2017). The average half-life of dexamphetamine is 10 to 12 hours (Mandelbaum, 2017, Markowitz & Patrick, 2017). Although amphetamine is at least a partial substrate of CYP2D6, there are no published clinical studies assessing the influence of a co-administered medication recognised as a CYP2D6 inhibitor (Markowitz & Patrick, 2017).

The submitted literature data are adequate to assess the non-clinical absorption, metabolism and elimination of dexamphetamine sulfate for the purpose of a well-established use application.

III.3 Toxicology

A single repeated dose toxicity study focusing on the neurotoxic effects of dexamphetamine shows that administration of escalating doses of dexamphetamine in rats did not result in the neurotoxic effects that are normally observed after administration of high doses of amphetamine, probably due to sensitisation (Robinson & Camp, 1987).

The main physiological and behavioural effect of repeated exposure to amphetamine in rodents was the development of tolerance (Abdallah, 1973; Lewander, 1968; Magour et al., 1974). The MAH added a section in the SmPC on the risk of dependence/abuse upon long term use of the product.
Considering the long-term clinical use of dexamphetamine, there is no indications that dexamphetamine has genotoxic potential. Literature suggests that genotoxicity studies (Ames test, chromosomal aberration assay in Chinese hamster ovary cells) did not show evidence of genotoxic potential (NTP, 1991; Zeiger et al., 1987).

A study in rat embryo cells did not result in effects indicating oncogenic potential (Price et al., 1978). The National Toxicology Program conducted 14-day, 13- week, and 2-year studies to determine the toxic and carcinogenic properties of dl-amphetamine sulphate. There was no evidence of carcinogenic activity of dl-amphetamine sulphate for rats or mice (NTP, 1991). In addition, no association with an increased cancer risk has been found in the long-term clinical use of dexamphetamine (Steinhausen & Helenius, 2013).

There is only limited data on non-clinical reproductive and developmental toxicity studies. A study with amphetamine in pregnant rats showed no treatment-related effects on litter parameters or malformations or in variations except for a possible increase in delayed cranial ossification sites (FDA, 2001; Golub et al., 2005). However, a study from 1979 showed that prenatal amphetamine exposure increased sexual receptivity in female rats (Golub et al., 2005; Ramirez et al., 1979).

Chronic exposure to high doses of amphetamines can induce tolerance or sensitisation in animals. High doses of amphetamines may induce neural toxicity (chromatolytic medulla neurons, swollen or reduced dopaminergic axons, and serotonin deficits). However, such doses may be not relevant for the therapeutically used doses of amphetamine, but more reflecting dosages used in abuse (Berman et al., 2009). This is acknowledged.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The log K_{ow} of dexamphetamine was experimentally determined (Lindeke et al., 1982). The partition coefficient for dexamphetamine was 1.69. As this is lower than 4.5, the substance is not considered to be screened for persistence, bioaccumulation and toxicity.
For the calculation of the $PEC_{surfacewater}$, the MAH has refined the F_{PEN} (market penetration factor), based on the prevalence of ADHD in 0-19 year olds. As Adhesa is indicated for ADHD medication users for whom methylphenidate is inadequate, this was taken into consideration for the revised F_{pen} as well. Although a more recent study (Cheung et al., 2020) was conducted, the fraction of methylphenidate users in 2012 was used as this concerned a worst case approach regarding the fraction of people that will use dexamphetamine. Following this approach, the PEC_{sw} (predicted environmental concentration in surface water) was calculated to be 0.00967 µg/L. As this is lower than the action limit of 0.01 µg/L, it is agreed that a Phase II assessment is not necessary.

However, for the ERA the following recommendations for actualisation are made:

- A refined F_{pen} was used for the calculation of the PEC_{sw}. The Applicant should verify whether the respective refined F_{pen} is still appropriate, and if not, update the F_{pen}

accordingly with the most recent F_{pen} (based on prevalence data not older than 5 years). This can be done for example, by assessing European disease prevalence data for the sought indication(s), published by a reliable and independent source (see Q6 of the current ERA guideline, p15/64). It is noted that the underlying reports and publications should be supplied as there is variation in disease prevalence over the EU and the F_{pen} should be calculated for the member state with the highest prevalence of the disease.

III.5 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dexamphetamine sulphate is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of the active substance, no new clinical data was submitted, instead the MAH submitted a clinical overview for the justification of the proposed indications and posology, which includes numerous publications. This is acceptable. An overview of the clinical aspects of dexamphetamine is given below.

<u>Bridging to the products described in the literature</u>
The products described in the literature are no longer available. Therefore, the bridging data submitted by the MAH was reassessed on a 'case-by-case' basis. See section “VI. Overall conclusion” for more information.

To support the bridging, the MAH has conducted several *in vitro* studies and submitted the results, supplemented with literature data. An overview of the reassessment of the submitted data is given below:

- Relevant comparator(s) for bridging to the literature studies:
  It is not easy to define the most relevant comparator from the supporting literature. The bulk of evidence for the efficacy and safety of dexamphetamine for the treatment of ADHD concerns several rather old, small sample size studies with cross-over design. A few studies can be identified which support the efficacy of dexamphetamine, i.e. Elia et al., 199) and Arnold et al., 1978, however it is doubtful whether these could be labelled as pivotal and are sufficient to establish efficacy without the presence of the other numerous studies. The composition of the dexamphetamine products used in

these two studies is unknown. Direct bridging would therefore likely require comparison to several products via dissolution testing (which is hampered by inadequate information regarding used products in the studies) or a comparison of pharmacokinetic data.

- Biopharmaceutical Classification System (BCS) and possible impact on bioavailability of Adhesa 5 mg tablets:
  Solubility data conform ICH M9 guideline (EMA/CHMP/ICH/493213/2018) show that the maximum single dose of 40 mg dexamphetamine sulphate is soluble in 250 mL pH buffer 1.2, 4.5, 6.8 and at 37±1°C. Dexamphetamine is a BCS Class III drug, which is a drug with high solubility and a low (less than 85%) absorption. The extent of absorption is not clear from the literature data and therefore the drug is classified as having a low permeability. Adhesa 5 mg contain excipients that are considered not critical for the absorption, in line with the ICH M09 guideline on biowaivers. Furthermore, dissolution results showed that dexamphetamine is very rapidly released (i.e. >85% within 15 min.) from the formulation at pH 1.2, 4.5 and 6.8. As such no issues with the availability of the drug for absorption in the gastro-intestinal tract are expected.

- Bridge by use of a similar formulation
  To obtain dissolution data representative for the products used in literature, the MAH manufactured a capsule formulation containing, apart from 5 mg dexamphetamine, lactose monohydrate, microcrystalline cellulose and colloidal silica. These excipients were also contained in several products mentioned in the literature data. Although the difference in excipients, dissolution data of this capsule formulation showed comparable dissolution with Adhesa 5 mg tablet (more than 85% within 15 min.) at pH 1.2, 4.5 and 6.8. This bridge is considered an indirect bridge, as no product from the literature is used.

- Bridge via Attentin (Amfexa)
  The MAH has submitted comparative dissolution study results vs. Attentin, which is mentioned in the submitted literature data. The studies are according to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guidelines. More than 85% of the label claim is dissolved within 15 minutes at pH 1.2, 4.5 and 6.8. Comparable dissolution profiles with this product have been shown. These data are considered supportive only as Attentin is used only in one of the submitted literature references, a study which is not considered pivotal.

In conclusion, excipients in Adhesa 5 mg tablets are not critical for absorption and dissolution data showed very rapid dissolution at pH 1.2, 4.5 and 6.8; as such no issues regarding systemic bioavailability are foreseen. Moreover, as an indirect bridge, comparable dissolution is shown to a self-made formulation which contains comparable excipients mentioned in literature. Additional supportive data by the use of Attentin, mentioned in literature but not considered pivotal, showed comparable dissolution. These data also indicate no issues with systemic exposure of dexamphetamine. Overall, these bridging data are considered sufficient to

demonstrate that the composition and release characteristics of the product applied for are comparable to the products described in literature.

IV.2 Pharmacokinetics

In accordance with the Directive 2001/83/EC (Annex I, part II) regarding article 10a applications, the MAH has demonstrated, using bridging data, that the product applied for is similar to those described in the literature (see section IV.1). The MAH has provided a well summarised pharmacokinetics overview, this is sufficient evidence to bridge the statements regarding the pharmacokinetics of dexamphetamine to the proposed formulation.

Absorption

Literature data show that t_{max} values after oral administration are obtained after about 2 – 4 hours. In general, pharmacokinetic studies conducted in normal adult volunteers indicate that the area under the plasma concentration– time curve (AUC) in the 24 hours postdosing ($AUC_{0–24}$) and the C_{max} are dose proportional (Markowitz & Patrick 2017). Considering the data of Perez-Reyes et al., 1992 and Pizarro et al., 1999, linear pharmacokinetic seems attained over the 5-40 mg dose range. The elimination half-life is about 10 hours, which increases in case urine is acidified or decreases in case urine is alkalised. Considering the elimination half-life of 10 hours and once or twice daily dosing, accumulation may be expected (Carvalho et al., 2012). However, dexamphetamine dose is titrated according to tolerability and degree of efficacy observed.

The effect of food on the absorption of dexamphetamine from Adhesa 5 mg has not been studied thus a possible effect of food on absorption cannot be excluded. Therefore, the SmPC recommends that Adhesa 5 mg should be taken in a standardised manner in relation to the timing of meals, i.e. that doses should be given at the same times, relative to the time of meals, on each day, preferably with or immediately after meals. This is considered appropriate.

Distribution

Protein binding of dexamphetamine is low, i.e. estimated to be about 16-20%. Dexamphetamine is widely distributed to the body and crosses the blood-brain-barrier. This relatively low protein binding is consistent with most of the drug in the bloodstream, subsequently accumulating in highly perfused organs. Accordingly, amphetamine is widely distributed throughout the body and readily penetrates the central nervous system (Childress et al., 2018; Markowitz & Patrick 2017). Concentrations achieved in the central nervous system can be 8 times higher than plasma levels (SPC Tentin, another registered dexamphetamine product), this information is also included in the SmPC of Adhesa.

Metabolism

Amphetamine undergoes stereoselective metabolism with d-AMP metabolised more rapidly than l-AMP, resulting in different exposures to each enantiomer. This is reflected by d-AMP having a $t_{1/2}$ that is approximately 2-3 hours shorter than l-AMP (e.g. 9–11 h for d-AMP and 11–14 h for l-AMP). Metabolism comprises hydroxylation and conjugation with glucuronic acid leading to more hydrophilic components which can be more easily eliminated. Smaller amounts of amphetamine are converted to norephedrine by oxidation (Childress et al., 2018).

Hydroxylation produces an active metabolite (p-hydroxynorephedrine) which acts as a false neurotransmitter and may account for some drug effects, especially in chronic users.
CYP2D6 is one of several enzymes involved in the biotransformation of amphetamines, which potentially mitigates the overall impact of CYP2D6 genetic variants on amphetamine disposition (Bach et al., 1999; Dring et al., 1970; Haufroid et al., 2015; Wu et al., 1997). The SPC indicates this in section 4.5 as follows: 'It is not known to which degree dexamphetamine metabolism is dependent on CYP enzymes. Co-administration of potent inhibitors or inducers of CYP enzymes should be made with caution.' This is acceptable.

Elimination
Dexamphetamine is excreted in the urine as unchanged parent drug together with some hydroxylated metabolites. Urinary excretion is depending on urinary pH, elimination is increased in acidic urine (Childress et al., 2019; Markowitz & Patrick 2017). Due to this, a wide range of urinary recoveries have been published.

Special patient groups
The influence of renal and hepatic impairment on the pharmacokinetics of dexamphetamine has not been specifically addressed. The SmPC indicates that there is no experience with the use of dexamphetamine in patients with renal or hepatic insufficiency. Therefore, dexamphetamine should be used with special caution in this patient group by taking care of titration and dosage. This is considered acceptable since dexamphetamine is indicated in patients aged 6-17 years old, normally a healthy population.

Interactions
Amphetamines can interact with a number of medications such as antihistamines (Okuda et al., 2004), tricyclic antidepressants (Garattini et al., 1976), serotonergic drugs (DeVane, 1999; Prior et al., 2002; Samara & Warner, 2017; Labellarte et al., 1998; Akingbola & Singh, 2012), neuroleptics and other drugs acting on catecholamines (Amphetamines 2016; Garattini et al., 1976), monoamine oxidase inhibitors (Amphetamines 2016) and halogenated narcotics (Vanderschuren et al., 2003, Sofuoglu et al., 2008; Dalal & Melzack 1998). There are also known non-specific interactions of amphetamines with compounds showing an inhibition of gastric emptying and intestinal motility, compounds that decrease or enhance the aromatic hydroxylation through liver microsomal enzymes and compounds that change the urinary pH (Garattini et al., 1976). Overall, the pharmacokinetic interactions discussed in the clinical overview are in line with those stated in the SmPC.

IV.3 Pharmacodynamics

Amphetamines increase the levels of catecholamines in the synaptic space by releasing dopamine and noradrenaline from dopaminergic neurons, blocking reuptake of noradrenaline and dopamine by pre-synaptic neurons, and possibly by inhibiting monoamine oxidase (Rizzo & Gulisano 2013).

The primary site of action is the cerebral cortex (Drug Monograph: Dextroamphetamine). The exact mechanism of action however in ADHD is not clearly understood. Literature references discussing the effect of dexamphetamine on cardiovascular system, mainly blood pressure and heart rate, in patients with ADHD and healthy volunteers has been submitted (Angrist et

al., 2001; Brauer & De Wit 1997; Drug Bank; Rush et al., 2001). These support the statements in the proposed SmPC regarding effects on blood pressure and heart rate, and their regular monitoring.

The proposed SmPC states that adrenergic blockers (e.g. propranolol), lithium, and α-methyltyrosine may attenuate the effects of dexamphetamine, but there is little evidence on this. However, considering that these interactions are established in the SmPCs of other dexamphetamine containing products in the RMS, they are accepted.

Furthermore, adequate literature has been provided to support the mentioned pharmacodynamic interactions in the SmPC, apart from halogenated narcotics. For this interaction, the MAH refers to the SmPC of Tentin, another registered dexamphetamine product, which is not appropriate within a WEU application. However, dexamphetamine is a sympathomimetic, and might be expected to increase the risk of hypertension if used with inhalational anaesthetics. Such warning is also known for methylphenidate. Therefore, the addition of this interaction and the accompanying advice to avoid dexamphetamine on the day of the surgery is accepted.

Overall, the MAH has provided an adequate overview of the mechanism of action of dexamphetamine and the discussion on pharmacodynamics is adequate, the necessary information is adequately included in the SmPC.

IV.4 Clinical efficacy

The MAH has presented a small selection of review articles and individual studies to support the efficacy of dexamphetamine in the treatment of ADHD in children. The literature search strategy and study selection is acceptable.

The discussed literature references concern mainly rather old, small sample size studies with cross-over design. Some of these, in particular of Elia et al., 1991 and Arnold et al., 1978 support the efficacy of dexamfetamine in the treatment of ADHD in children and adolescents. It is also noted that the large network meta-analysis of Catala-Lopez et al., (2017) supports the efficacy claim for amphetamines as a class. However, as also pointed out by the authors, the evidence is of low quality and the meta-analysis only includes 2 studies with dexamfetamine, both without a placebo control.

Some references can be considered only supportive, as they provide very little data for dexamphetamine specifically, as the majority of data concern other stimulants. Effects

observed with lisdexamfetamine cannot be readily extrapolated to dexamphetamine as the substances differ in their potency.

It is acknowledged that several current therapeutic guidelines do list dexamphetamine as a valid pharmacologic treatment option for ADHD and another dexamphetamine containing product is registered in the RMS for the sought indication.

Altogether the provided clinical overview supports the efficacy of dexamphetamine in the treatment of ADHD in children and adolescents adequately in the context of demonstrated well-established use.

The product has a functional score line, which allows smaller titration steps than the 5 mg steps. This may be beneficial, allowing more individually adjusted dosing according to response. The MAH has discussed the available data supporting smaller titration steps as requested. Also, several current treatment guidelines (National Institute for Health and Care Excellence (NICE), 2018; Canadian ADHD Resource Alliance (CADDRA), 2020; Young et al., 2020) acknowledge the need for more careful titration in patients with comorbidities. However, the available data is too sparse to make specific recommendations in subgroups (NICE 2018). Therefore, only a general recommendation on slower and lower titration can be made. Based on this, remarks were included in the SmPC to emphasise that the score line is only to simplify breaking so that swallowing is easier, not to divide the tablet into equal doses (section 3) and that careful dose titration based on patient response is necessary when initiating treatment with dexamphetamine. Considering the above and the availability of functional score line, the possibility of smaller titration steps has been included in the SmPC section 4.2.

The sought indication as second line treatment after methylphenidate is in line with current treatment guidelines within the EU as well as other registered dexamphetamine products in the RMS, and therefore accepted.

IV.5 Clinical safety

The MAH has presented prevalence and incidence figures for ADHD in the clinical overview, worldwide and specifically in some EU member states.
Exposure data on dexamphetamine is limited, however dexamphetamine is amongst the top four most used ADHD medications in children and adolescents in Europe.
The most common adverse events, which dexamphetamine shares with other drugs in the stimulant class are decreased appetite, insomnia, abdominal pain, nausea, changes in blood pressure and pulse and headache.

Relevant literature regarding the safety aspects of the product was submitted and sufficiently discussed by the MAH. The necessary information was adequately addressed in the SmPC on the risks, symptoms of overdose, contraindications, adverse effects characteristics of the pharmacological class, patient exposure, long term safety and safety in special populations. Furthermore, measurements for pre-treatment screening and on-treatment monitoring are also included in the SmPC. The proposed SmPC is acceptable. As the product is a medicinal drug with high risk of abuse, misuse and diversion, not all proposed pack sizes have been

accepted. As a risk minimisation measure, the MAH has limited the pack size to a maximum of 100 tablets.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, 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 Adhesa. At the time of approval, the most recent version of the RMP was version 003, date of final sign 27 June 2022.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Drug abuse / drug dependence • Drug misuse and diversion • Cardiac and cardiovascular disorders, incl. increased blood pressure versus hypertension and increased heart rate, tachycardia, arrhythmias • Cardiomyopathy • Increased risk of depression • Increased risk of aggressive / hostile behaviour • Psychotic reactions, e.g. hallucination (visual, auditory, skin sensation) and mania • Withdrawal syndrome • Decreased rate of growth and development / anorexia • Serious skin reaction
Important potential risks	• Ischaemic / serious cardiovascular events, e.g. myocardial infarction, sudden death, cyanosis, QT prolongation • Cerebrovascular disorders, e.g. stroke (ischaemic and haemorrhagic) • Migraine • Raynaud's syndrome • Suicidal ideation • Tics / Tourette's / dystonia's • Repetitive behaviours • Seizures and Epilepsy • Delayed sexual maturation and neonatal growth • Neonatal toxicity, e.g. cardio-respiratory toxicity • Carcinogenicity • Overdose • Off-label use

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

At the time of approval of this product, it was considered that additional risk minimisation measures are necessary for the safe and effective use of the product. For this, the MAH proposed additional risk minimisation measures (including educational material). These are in line with those of the already approved products Attentin/Amfexa/Tentin and are therefore accepted. The material for additional risk minimisation measures have already been implemented and are available online together with the package leaflet and the SmPC on the relevant websites.

Additional Risk Minimisation Measures (including educational material)

The following measures are added to minimise risks:

- A physician's guide to prescribing stimulant medication.
- Pre-screening and on-going monitoring recommendations of patients' blood pressure, heart rate, growth (weight, height, appetite) and emergence of psychoses.

Educational materials will be submitted by the MAH to the competent authorities of Member States and the content and implementation of educational materials should be agreed on national level with the competent authority prior to launch. The educational material contains the following key elements:

Approved key messages of the additional risk minimisation measures:

- Prescriber checklist:
  - Lists of tests to be conducted for the initial screening and monitoring of the patient
  - Special warnings and precautions for use
  - Measurement recording chart.

- Guide for healthcare professionals:
  - Information on Dexamface, including the approved indication according to the SmPC
  - Remarks on the importance of reporting of adverse events
  - Details on how to minimise the risk of drug abuse / drug dependence, drug misuse and diversion, and off-label use (signs and symptoms, patient screening and monitoring).

- Parent/carer guide:
  - A description of the important identified/potential risks associated with the use of Dexamface namely: drug abuse / drug dependence, drug misuse and diversion, off-label use
  - A description of the signs and symptoms of the identified/potential risk of drug abuse / drug dependence, drug misuse and diversion, and off-label use
  - A description on how to prevent the important identified/potential risks of drug abuse / drug dependence, drug misuse and diversion, and off-label use.

- Follow-up form for reporting side effects.

IV.7 Discussion on the clinical aspects

This procedure concerns a well-established use application for dexamphetamine. For this authorisation, reference is made to literature. No new clinical studies were conducted. The clinical benefit of treating ADHD with dexamphetamine is well known. The MAH has adequately summarised the bibliographical efficacy data in the clinical overview using relevant literature for the use of dexamphetamine in child and adolescents. Furthermore, the risk management is adequately addressed. Overall, the clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Amfexa 5 mg tablets, RVG 125714 SE/H/1719/001. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Adhesa 5 mg tablets has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

The provided clinical overview supports the efficacy of dexamphetamine in the treatment of ADHD in children and adolescents adequately in the context of demonstrated well-established use. Well-established use of dexamphetamine in the sought indication has been adequately justified. Bridging of the product applied for to the used literature is considered considered established. From a clinical point of view, the indications as well as the posology of the new product are in line with the use and recommendations of the innovator, which has been registered for more than ten years in the RMS. Based upon clinical data and the longstanding

clinical experience, the use of dexamphetamine in the proposed indications can be considered well-established with demonstrated efficacy and safety.

The marketing authorisation for this product was initially requested via a decentral procedure (NL/H/5396/001/DC) based on Article 10a of Directive 2001/83/EC with the Netherlands as Reference Member State and Germany as concern member state. The application was discussed in the Board meeting of 28 Juli 2022 (nr. 1008) and in a breakout session (BOS) held in August 2022. After this, the procedure was finalised with a negative outcome, as appropriate bridging (direct bridging) was not established between the new product and the products described in the used literature. Instead, 'indirect bridging' was used via a product that was described in too little detail (non-pivotal) in the literature. For this, the MAH submitted dissolution data comparing Adhesa with an in-house manufactured capsule-product that approximates the products reported in the used literature. Additionally, the MAH provided argumentation for this approach, justifying why any small differences would not be relevant. See the Public assessment report for NL/H/5396/001/DC.

The applicant submitted an official objection against this decision, which was followed by an oral hearing in March 2023 between the applicant and a delegation from the Dutch Medicines Evaluation Board (MEB). During the hearing, the grounds for objection, substantiated with relevant information, were discussed.

The MAH argumentation was assessed and it was concluded that direct bridging is not specifically required in the European guidelines (Notice to Applicants). The CMDh, which assesses these types of cases on a case-by-case basis, also has no policy in this area. Overall, the objection was well-founded as there is no standing policy on direct bridging. Consequently, a case-by-case reassessment was carried out within the applicable legal framework, considering the data as a whole and in the specific context.
The following conclusion was drawn:
Based on Article 10a of Directive 2001/83/EC, it has been shown that the balancing of benefits and risks of the requested medicine is beneficial and that it has the stated therapeutic effect. This, taking in to account the applicable administration form, excipients, BCS classification of the active substance, dissolution behaviour and the comparison data (incl. indirect bridging) with other dexamfetamine-containing medicines. Based on these considerations, the application is considered approvable and the objection is declared well-founded. The bridging data provided is sufficient to demonstrate that the composition and release characteristics of Adhesa are comparable to the products described in literature.

A marketing authorisation was subsequently granted and the product was nationally registered in the Netherlands with marketing authorisation number RVG 128087 on 27 July 2023. After this, the product was registered in the additional CMS on 13 August 2025, via the current mutual recognition procedure NL/H/6293/001/MR.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/6293/001/MR	MRP request	Yes	22-10-2025	Approved	N.A.