Annex II

Scientific conclusions and grounds for positive opinion presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Dexamed (see Annex I)

Dexamfetamine, (2S)-1-phenylpropan-2-amine, is the dextrorotatory, stereoisomer of amfetamine. It is a Central Nervous System stimulant, more potent than the racemic mixture. Amfetamines increase levels of catecholamine in the synaptic cleft by blocking reuptake of noradrenaline and dopamine by presynaptic neurons, by releasing dopamine and noradrenaline from dopaminergic neurons, and possibly by inhibiting monoamine oxidase. There is also evidence that amfetamines increase release and turnover of serotonin.

Dexamfetamine is currently used for treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD) in several EU countries including the reference Member State (RMS) in this procedure. Its mechanism of action in ADHD is not fully understood, but its efficacy in treatment of ADHD has not been disputed during this procedure. An agreement has been reached during the CMDh procedure that dexamfetamine has efficacy in ADHD which is in no way inferior to the other stimulants.

However there are perceived risks of diversion and abuse associated with this medication. Therefore as a measure to mitigate this risk, the applicant proposed to downgrade dexamfetamine to second line use in ADHD and for children and adolescents of 6 to 17 years of age, if other medicinal and non-medical treatment options have not achieved adequate results. .

In addition the applicant proposed to undertake a drug utilisation study (DUS) to monitor for reports of abuse and/or overdose, and a non-interventional post authorisation safety study (PASS) to monitor key adverse events. Furthermore educational materials would also be made available for both physicians and patients, including the provision of checklists, and are in line with those for other ADHD medicines.

At the final CMDh discussion, there were two major issues where agreement could not be reached by Member States. The CHMP was therefore asked to consider:

- Whether downgrading the product to second line treatment and the proposed RMP measures are sufficient to mitigate concerns relating to the perceived potential for misuse and diversion.
- Whether sufficient scientific and clinical evidence exists to support the use of the product as second line treatment of ADHD.

Efficacy in second line treatment of ADHD

The present application for Dexamed as second-line treatment of ADHD is a bibliographic (well-established use) application. Therefore, the assessment of efficacy is based on an intensive literature search as well as on current European treatment guidelines. This is acceptable as in well-established use applications it is not required that applicants provide results of pre-clinical tests and clinical trials, these are to be replaced by appropriate scientific literature.

Clinical studies show that there are ADHD patients who respond to methylphenidate and not to dexamfetamine and vice versa. The study by Elia et al. (1991) concluded that there is a need to try both stimulants because there is individual variability in response. The reason for the different responses could be different pharmacological mechanisms of action. Methylphenidate reversibly binds to the presynaptic transporter protein with resultant inhibition of catecholamines re-uptake into the presynaptic neuron (Volkow et al., 2002), increases the release of dopamine from presynaptic cytoplasmic storage vesicles and blocks the uptake of dopamine into neuronal cytoplasmic storage

vesicles, making dopamine more available in the presynaptic cytoplasm for release into the synaptic cleft (Sulzer et al., 2005).

In the Elia et al. study, approximately 30% of participants did not respond to one treatment but only 4% were non-responders to both. While there is no information about the sequence of treatments, mainly due to its cross-over design the results are convincing. There are, however, methodological problems with this study. The number of patients was small and the statistical significance of the findings is uncertain. In addition, this was an independent study published in 1991 which precludes the assessment of the original data. The CHMP therefore considered that this publication can be regarded as supportive of efficacy but does not provide conclusive evidence.

These data are further supported by the Arnold et al. (1978) study. More importantly, the Arnold LE (2000) comparative review analysed six non-duplicative studies, from which a response rate of 66% was calculated for dexamfetamine sulphate, 56% for methylphenidate and 85% stimulant response if both are tried. The author concludes that the individual patient response profiles are non-congruent, and that non-response or intolerable side effects with one stimulant do not preclude a good response to the other. While the review has methodological limitations, the conclusions reached are based on relevant evidence. This publication also includes a comprehensive review of the preclinical pharmacodynamics of the two compounds, which may help explain the observed variability in response. It concludes that methylphenidate is more selective for dopamine transporter, while dexamfetamine also has a number of other actions including direct actions on receptors and modulating other modes of dopamine uptake as well as effect on other catecholamines.

Ramtvedt et al. (2013) have reported that in a cross-over clinical study including 36 children with a diagnostic of ADHD (as per Norwegian diagnostic guidelines), who received, in sequence, 2 weeks each of methylphenidate, dexamfetamine and placebo, dexamfetamine and methylphenidate each produced a favourable response in 26 children (72%), but not always the same child. However, the number of responders increased to 33 (92%) after both stimulants were tried. From the publication alone it is difficult to assess the meaningfulness of the suggested effect sizes based on which the level of response was assessed, but despite some lack of clarity regarding methodology it is noted that the conclusions are in line with those of the Elia et al. study.

In addition, at least seven evidence-based guidelines for the pharmacological treatment of ADHD recommend dexamfetamine as first-line therapy; others give an explicit favourable recommendation for use as a therapeutic option in ADHD (Seixas et al., 2012). It is noted that all the guidelines mentioned in this article are from countries where dexamfetamine is already marketed for ADHD.

Lastly, it is noted that lisdexamfetamine is an inactive prodrug which is absorbed to the bloodstream where it is gradually converted to dexamfetamine. Lisdexamfetamine was recently approved in some Member States as part of a comprehensive treatment programme for ADHD in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. Lisdexamfetamine and dexamfetamine can be regarded as pharmacodynamically identical, therefore to grant a marketing authorisation for dexamfetamine as second line ADHD treatment would be consistent with the recent approval of lisdexamfetamine for use in the same population.

Taking into account all the available data, the Committee considered that there is sufficient evidence to conclude that non-responders to methylphenidate may benefit from dexamfetamine. The two substances have similar efficacy in ADHD but different mechanisms of action. Methylphenidate is more selective for the dopamine transporter, while dexamfetamine also has a number of other actions including direct actions on receptors and modulating other modes of dopamine uptake as well as effect on other catecholamines. Even though no single study can be taken as pivotal evidence, the publications submitted within the application, which include not just published studies but also therapeutic guidelines and textbooks, are supportive of the efficacy in second line treatment of ADHD.

Risk for abuse and dependence

During the assessment of the marketing authorisation application for Dexamed, concerns were raised regarding the potential for abuse and dependence of dexamfetamine. The objecting Member State considered that, based on the pharmacodynamics and pharmacokinetics of dexamfetamine, the potential risk for dependence and abuse associated to this product is higher than that of other treatment options for ADHD.

Indeed it is agreed that stimulants, including dexamfetamine, have potential for misuse, diversion and dependence. However the efficacy of dexamfetamine in the treatment of ADHD is not disputed. In the current application, the use of dexamfetamine as second line treatment of ADHD is a measure introduced to mitigate this concern. The indication also includes a statement that treatment should be initiated and regularly evaluated by a physician with specialist expertise in child and adolescent mental health after a comprehensive assessment has led to a diagnosis of ADHD. These and the other measures in the risk management plan are proposed to ensure that dexamfetamine is only made available to patients who really need it and can benefit from it, therefore mitigating the risk of misuse and diversion.

With regards to the risk of misuse and diversion within the ADHD population, a meta-analytic review by Lee et al. (2011) concluded that ADHD patients are at a considerably higher risk for substance abuse as compared to the (age-matched) general population. In other publications, authors seem to have further concluded that ADHD treatment with stimulants during childhood is associated with a reduction in the risk of substance use disorder later in life (Biederman et al. 1999; Wilens et al. 2003). However, a more recent meta-analysis by Humphreys et al. (2013) investigated both published and unpublished reports on a total of 15 different studies and concluded that effective treatment of ADHD, typically using methylphenidate, does not seem to have impact of substance abuse later in life. This meta-analysis identified a number of key issues that may explain the differences in outcome of the studies, and the authors noted that, while building on that of Wilens et al. (2003), is still relatively modest in terms of number of studies included. Therefore it is currently unclear whether treatment of ADHD patients with stimulants alters their risk of substance abuse disorder later in life, but evidence seems to indicate that the risk in the stimulant treated ADHD population is not higher than in the not treated ADHD population.

During the procedure the MAH conducted further research in the literature, online, in databases from European Health Authorities and WHO and its own safety database. Although it is acknowledged that misuse, abuse, dependence and diversion are events that will not always be reported to the prescribers, the search retrieved a very low event rate in the countries where dexamfetamine is available on the market for ADHD.

It is noted that age can be a dominant factor in substance use disorder. Experimentation with recreational drugs generally starts during adolescence, whereas treatment of ADHD can begin at an earlier age. In addition, ADHD patients are prescribed stimulants after an ADHD diagnosis has been made as opposed to deliberately seeking stimulants. It is acknowledged that abuse and dependence may occur, however there appears to be a difference between the population that abuses stimulants and the general ADHD population. The experts consulted expressed the fact that ADHD is less likely to produce euphoria in children when the products are used as intended. The experts were of the opinion that there is currently little evidence to suggest that dexamfetamine is associated with a higher risk of dependence in the treated ADHD population than in those without ADHD.

Moreover short acting treatments are expected to have some advantages compared to long-acting treatments. Indeed short acting treatments are less likely to affect sleep pattern and appetite compared to long-acting products. Treatment optimisation may be also easier to achieve with

immediate-release forms when an initial titration phase is needed to determine the correct dosing levels.

The Committee also noted that dexamfetamine-containing products have been available in the EU for several years without a risk management plan and therefore the introduction of a dexamfetamine product with a risk management plan is expected to represent a significant improvement for patients.

Risks associated with long term use

With regards to other potential risks associated with long-term use of dexamfetamine such as possible impairment of neuro-cognitive development and risk of cardiomyopathy, there is no clinical evidence to support that long-term treatment has any negative influence on neuro-cognitive development. However it is noted that overall very few data is available in clinical practice to support this. The identified risk of cardiomyopathy is mainly associated with chronic use, especially with high dose use. The experts' panel recognises this risk but considers its frequency to be low. It was noted that increased blood pressure may occur as well as tachycardia. In addition to specific measures in the risk management plan, the committee recommended the monitoring of blood pressure and pulse rate in order to minimise these risks.

Taking into account all the available data, the Committee accepted that dexamfetamine has potential for misuse, diversion and also dependence. However, the Committee also considered that the risk minimisation measures proposed are appropriate to mitigate the risk. The indication has been restricted to second line, the risk management plan for the product includes educational material for both prescribers and patients/carers, as well as a drug utilisation study that has been expanded to collect information specifically on abuse and misuse. All of these measures, taken together with existing national laws concerning manufacture, distribution and prescription of controlled drugs are considered to balance the risk.

Risk management plan

The proposed risk minimisation measures are a combination of routine activities (inclusion of warnings in the product information) and the following educational materials and tools:

- A physician's guide to prescribing including direction for diagnosis according to DSM/ICD guidelines and for recognition and exclusion of patients with a history of abuse misuse diversion and dependency;
- Checklists for pre-screening and on-going monitoring of patients' blood pressure, heart rate, growth (weight, height, appetite) and emergence of psychoses.

During the assessment of the application at Member State level, advice from the PRAC on the risk management plan was sought and the applicant agreed with the recommendation to:

- Undertake a DUS to follow the use of prescribed dexamfetamine in the European Union using multiple data sources. In addition, the DUS should be expanded to actively obtain reports of abuse, misuse, diversion and dependence in children with ADHD from poison centres, drug monitoring centres, other databases, publicly available information in the literature and online.
- Conduct a PASS to evaluate the long-term safety profile of dexamfetamine in children with ADHD, specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events. This retrospective (new users) study will also compare the relative risk between dexamfetamine and other stimulants in the patient population.

In addition, the CHMP recommended that the risk management plan should be further updated (see annex IV).

During the referral procedure, the CHMP recommended safety related changes to the product information:

- Amendment to the section 4.1 to advise that “Treatment should be under the supervision of a specialist in childhood and/or adolescent behavioural disorders.” and that “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.”
- Introduction of a statement in section 4.4 on “Abuse, misuse, and diversion” reporting that the risk is generally greater for short acting stimulants than for corresponding long-acting products.
- Introduction of a statement in section 4.8 on reporting of suspected adverse reactions.

The relevant sections of the product information were updated accordingly.

The CHMP, having considered the data submitted in the application is of the opinion that the above risk management activities are necessary for the safe and effective use of the medicinal product.

Overall benefit-risk balance

Having considered the data submitted by the applicant, the CHMP considered that there is sufficient evidence to conclude that non-responders to methylphenidate may benefit from dexamfetamine. The clinical data available, when taken together with clinical guidelines and the fact that the mechanism of action is different from that of other therapeutic options, supports the efficacy of dexamfetamine in second line treatment of ADHD.

It is accepted that dexamfetamine has potential for misuse, diversion and also dependence. Its use as second line treatment only, despite its proven efficacy, is a measure introduced in order to mitigate this concern. The indication also includes a statement that it should only be prescribed by a specialist when the patient has been diagnosed with ADHD following comprehensive assessment of chronicity and severity according to DSM or ICD guidance and only when methylphenidate treatment has proved ineffective. During treatments regular evaluations should be performed regarding treatment necessity (see below) and possible occurrence of overuse, dependence or diversion.

Overall, the Committee considered that the risk minimisation measures proposed to mitigate the risk of abuse are appropriate. The risk management plan for the product includes educational material for both prescribers and patients/carers, as well as a drug utilisation study that has been expanded to collect information specifically on abuse and misuse. All of these measures, taken together with existing national laws concerning manufacture, distribution and prescription of controlled drugs are considered to balance the risk.

The CHMP took note of the fact that the proposed RMP is in line with existing risk management plans for other stimulants (methylphenidate and lisdexamfetamine), and also that dexamfetamine-containing products have been available in the EU for several decades without a risk management plan. Therefore the introduction of a dexamfetamine product with a risk management plan is expected to provide significant improvement by collecting information about use of the product in real life setting, as well as introducing risk minimisation measures that are currently not in place.

Grounds for positive opinion, amendments of the summary of product characteristics and package leaflet, and conditions to the Marketing Authorisations

Whereas,

- The Committee considered the notification of the referral triggered by the United Kingdom under article 29(4) of Directive 2001/83/EC. The Netherlands considered that the granting of the marketing authorisation constitutes a potential serious risk to public health.
- The Committee reviewed all the data submitted by the applicant in support of the efficacy of dexamfetamine in second line treatment of ADHD, and the proposals for mitigation of the risk of misuse and diversion.
- The Committee is of the opinion that dexamfetamine has a mechanism of action different from that of methylphenidate, and that the available data is supportive of the efficacy of dexamfetamine in treatment of ADHD.
- The Committee is also of the opinion that the proposed risk minimisation measures are appropriate to mitigate the risks of misuse and diversion. A drug utilisation study to follow the use of prescribed dexamfetamine in the European using multiple data sources was also required. Furthermore the Committee requested that a PASS will be conducted to evaluate the long-term safety profile of dexamfetamine in children with ADHD, specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events.

Therefore, the CHMP was of the opinion that the benefit/risk ratio of Dexamed and associated names is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisations for which the summary of product characteristics and package leaflet are as set out in Annex III of the CHMP opinion and conditions to the marketing authorisations in Annex IV of the CHMP Opinion for Dexamed and associated names (see Annex I).