Translation of academic medicinal products towards clinical practice

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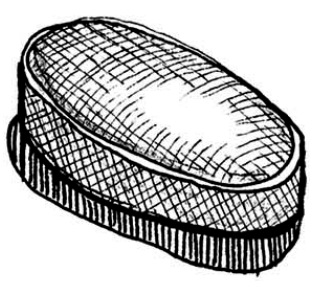

CHAPTER 8

The possibility of obtaining marketing authorization of orphan pharmaceutical compounding preparations: 3,4-DAP for Lambert-Eaton Myasthenic Syndrome

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Abstract

Pharmaceutical preparations, produced by (hospital) pharmacies, usually do not have marketing authorization. As a consequence, some of these pharmaceutical preparations can be picked-up by a pharmaceutical company to retrieve marketing authorization, often leading to price increases. An example is the 3,4-diaminopyridine slow release (3,4-DAP SR) tablets for Lambert-Eaton Myasthenic Syndrome (LEMS). In 2009 marketing authorization was given for the commercial immediate release phosphate salt of the drug, including a fifty-fold price increase compared to the pharmaceutical preparation. Obtaining marketing authorization for 3,4-DAP SR by academia might have been a solution to prevent this price increase. To determine whether the available data of a pharmaceutical preparation with long-term experience in regular care are adequate to retrieve marketing authorization, 3,4-DAP SR is used as a case study.

A retrospective qualitative case-study was performed. Initially, document analysis was executed by collecting the required data for marketing authorization in general and whether data of Firdapse® and 3,4-DAP SR met these requirements. Secondly, the (non-) available data of the two formulations were compared with each other to determine the differences in availability.

At the time of approval, almost all data were available for both Firdapse® and 3,4-DAP SR. Conversely, much of the data used for the approval of Firdapse® originated from the 3,4-DAP immediate release (3,4-DAP IR) formulation. Only two bioequivalence studies and one pharmacology safety study was performed with Firdapse® before marketing authorization application.

In conclusion, at time Firdapse® retrieved approval, the data available did not differ substantially from 3,4-DAP SR, indicating that approval with 3,4-DAP SR would have been possible. We make a plea for approval of orphan medicinal products developed and manufactured by academic institutions as to keep utilization of these products affordable.

Introduction

The Lambert-Eaton Myasthenic Syndrome (LEMS) is an ultra-orphan autoimmune disease of the neuromuscular junction[1,2] with a prevalence of 0·35:100 000[3,4]. Currently, due to lacking curing treatment of LEMS, symptoms can be relieved by preferably symptomatic or immunomodulating treatment[5]. 3,4-Diaminopyridine (3,4-DAP) is the most frequently prescribed symptomatic treatment and is used globally[6].

Until 2009, two formulations of 3,4-DAP tablets used to be available as pharmaceutical preparations: 3,4-DAP base immediate release (3,4-DAP IR) and 3,4-DAP base slow release (3,4-DAP SR). However, in 2009 a third type of 3,4-DAP received marketing authorization in Europe, Firdapse®[7], an immediate release phosphate salt, see table 1. Due to the licensed status of Firdapse® and the obtained orphan designation status, including ten years of market exclusivity, the two other 3,4-DAP formulations were not allowed anymore for treating LEMS in most countries despite the fact that before the licensed Firdapse® appeared, 3,4-DAP IR had obtained long-term experience in LEMS patients[8,9]. Likewise, the SR variant of 3,4-DAP has been produced and used for over 20 years at the Leiden University Medical Center (LUMC) in The Netherlands.

Table 1. Different formulations of 3,4-diaminopyridine. 3,4-DAP IR = 3,4-diaminopyridine immediate release, 3,4-DAP SR = 3,4-diaminopyridine slow release

Name	Base/phosphate	Immediate/slow release	Trade Name
3,4-DAP IR	Base	Immediate	NA (pharmaceutical preparation)
3,4-DAP SR	Base	Slow	NA (pharmaceutical preparation)
3,4-DAP phosphate	Phosphate	Immediate	Firdapse®

For Firdapse®, obtaining complete data for marketing authorization submission was not possible due to the rarity of the disease. Therefore, this medicinal product is approved 'under exceptional circumstances'[7]. After the approval of Firdapse®, a substantial increase in pricing occurred compared to the costs for the available pharmaceutical preparations 3,4-DAP SR and IR[10]. This rise in costs negatively influenced regular LEMS patient care: e.g. in the United Kingdom, due to the 50-fold increase in costs, health care insurances were not willing to pay these extra costs, while the pharmaceutical formulations were forbidden to be provided to patients, resulting in inaccessibility of 3,4-DAP as a treatment for LEMS patients[11,12]. Alternatively, in The Netherlands the Dutch Minister of Health, Welfare and Sport decided that due to the modified release profile of the SR formulation and the undesirable additional costs of Firdapse®, estimated at €1·8 million per year for the 40-70 treated patients, 3,4-DAP SR was still allowed for the treatment of LEMS patients[10].

Several pharmaceutical preparations, such as 3,4-DAP IR and SR, are produced in the (fully Good Manufacturing Practices (GMP) licensed hospital) pharmacies. In most cases, these are medicinal products for (ultra-) orphan diseases and arise from *ad hoc* preparations. Sometimes, in case such *ad hoc* preparation is prescribed more frequently, these preparations can be scaled up to (small) for-

hoc preparation is prescribed more frequently, these preparations can be scaled up to (small) for-stock preparations[13]. These for-stock preparations increase the requirements for documentation of the product and its quality assurance and lead to substantial experience with such medicinal products in regular care "Unpublished Observations, S. de Wilde *et al."*[13]. However, these unlicensed pharmaceutical preparations can easily be picked up by the pharmaceutical industry, and in some cases receive a license with a substantially higher price tag in comparison with the pharmaceutical preparation formulation[12]. 3,4-DAP SR is an example of such pharmaceutical preparation which was picked-up by the industry and for which the costs increased tremendously, but other examples exist, such as ibuprofen for neonatal patent ductus arteriosus and zinc acetate for Wilson's disease[14].

Licensing of a medicinal product guarantees a level of quality, efficacy, and safety of the product. Moreover, industrial production is more rigidly monitored compared to pharmaceutical preparations[13]. Due to this extra monitoring, it is reasonable that the costs for treatment increase compared to the regular therapy with pharmaceutical preparations. However, due to the ten years market exclusivity and the small market size, prices for (ultra-) orphan drugs often rise more than desired[15,16]. In some cases, the increase can be disproportionate to the limited efforts required for authorization[17], especially when (hardly) no original research is performed by the pharmaceutical company to obtain marketing authorization.

To determine whether the available data of a pharmaceutical preparation with long-term experience in regular clinical care are sufficient to apply for marketing authorization, 3,4-DAP by LEMS is used as a case study. The available data of 3,4-DAP SR will be compared with the data of the licensed Firdapse®, to investigate whether 3,4-DAP SR could have been licensed at the same time as Firdapse® did and/or which additional studies are still required to retrieve marketing authorization with 3,4-DAP SR. The goal of investigating marketing authorization possibilities for the pharmaceutical preparation 3,4-DAP SR is to guarantee regular patient care at a reasonable price. Recommendations will be provided to ensure reasonable pricing and possibilities of pharmaceutical preparations towards marketing authorization.

Methods

Study design

A retrospective qualitative case-study was performed with 3,4-DAP SR and Firdapse®. Initially, a document analysis was conducted to collect the required data for marketing authorization and whether Firdapse® and 3,4-DAP SR met these requirements. Secondly, the available data for the two formulations were compared with each other, to determine at which points the data of 3,4-DAP SR differed from the data of Firdapse®.

Processing and analysis of the data

Based on the requirements for an assessment report (AR)[18–20], data of Firdapse® in the AR were scored on availability[7]. When data were adopted in the AR, a check on the origin of the data was performed, including whether data came from the phosphate salt (Firdapse®) or from the 3,4-DAP IR. In case data were not available but were required after approval by the European Medicines Agency (EMA), this was also scored.

Above described method was also used for the unlicensed 3,4-DAP SR. Not only the pharmaceutical product dossier of 3,4-DAP SR was examined "Unpublished obeservations, M.G.H. de Jong, S de Wilde, K.J.M. Schimmel" but also the sources PubMed and Scopus were used to search for additional data, such as non-clinical and clinical pharmacokinetics and non-clinical toxicology.

Finally, data for both formulations were compared to determine whether the available data of 3,4-DAP SR differed from the data used for licensing of Firdapse®. Eventually, it was determined whether additional research would have been necessary for marketing authorization of 3,4-DAP SR, see figure 1. The scored data were subcategorized in quality (see supplementary 1), non-clinical (see supplementary 2) and clinical aspects (see supplementary 3) like the AR of Firdapse®.

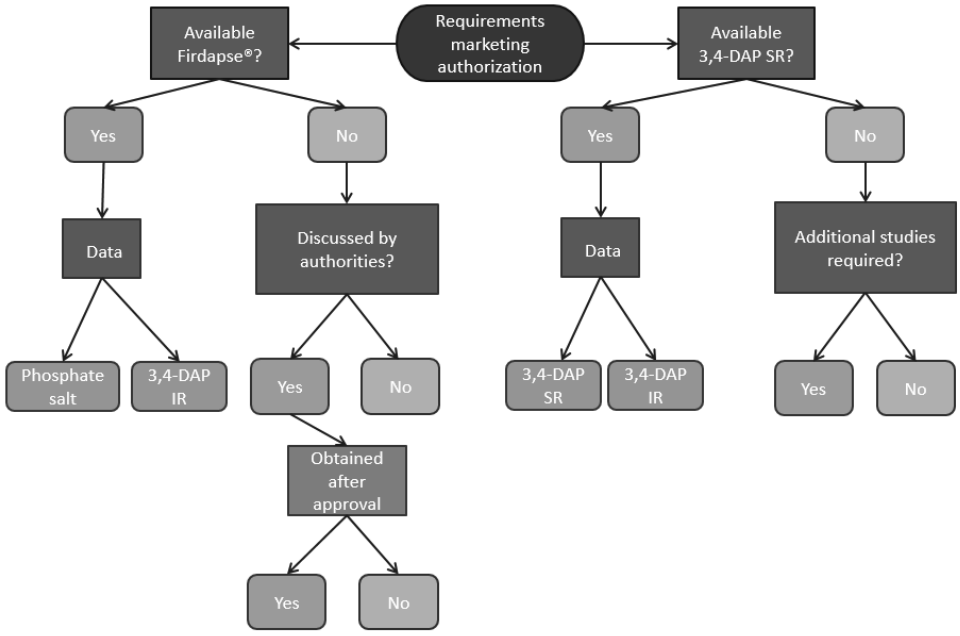

Figure 1. Schematic overview of the methodological analysis. 3,4-DAP = 3,4-diaminopyridine; IR = immediate release; SR = slow release.

Results

Overviews of the available data of Firdapse® in the AR and of 3,4-DAP in the product dossiers are listed in appendices 1-3, and a summary of missing data for both products is shown in table 2.

Quality

All required quality data, according to the requirements for marketing authorization, were available for both Firdapse® and 3,4-DAP SR (see supplementary 1). For 3,4-DAP SR, the data were less extensively described compared to Firdapse® but the data met the requirements (see supplementary 1).

Table 2. Missing data of Firdapse® and 3,4-DAP SR in the EPAR or product dossier. 3,4-DAP = 3,4-diaminopyridine; EPAR = European public assessment report; IR = immediate release; SR = slow release.

		Missing data	
		Firdapse®	**3,4-DAP SR**
Quality		-	-
Non-clinical	*Pharmacology*		Safety pharmacology programme
		Pharmacodynamic drug interactions	Pharmacodynamic drug interactions
	Pharmacokinetics		Distribution
		Metabolism	Metabolism
		Excretion	Excretion
		Pharmacokinetic drug interactions	Pharmacokinetic drug interactions
	Toxicology	Carcinogenicity	Carcinogenicity
			Reproduction toxicity
			Toxicokinetic
Clinical	*Pharmacokinetics*	Data obtained after approval	No data
	Pharmacodynamics	Secondary pharmacology	Secondary pharmacology
	Efficacy and safety	Available data and 3,4-DAP IR data	Available data and 3,4-DAP IR data

Non-clinical

The primary and secondary pharmacodynamic data were available for both formulations. However, data about the pharmacodynamic drug interactions for both medicinal products were lacking, see supplementary 2. Moreover, for 3,4-DAP SR the safety pharmacology programme was also missing. For both medicinal products data were adopted from the IR formulation of 3,4-DAP and both in vitro data and secondary pharmacodynamic data acquired from 3,4-DAP IR were described in the AR of Firdapse® and could be extended for 3,4-DAP SR. Also, data from 3,4-DAP IR, obtained from literature, was used for the in vivo data of 3,4-DAP SR[21,22].

Limited pharmacokinetic data were available for both product formulations, and absorption data were available for both medicinal products, see additional file 2. As for metabolism and excretion, no studies have been performed. Distribution data were only available for Firdapse®.

For Firdapse®, only carcinogenicity data were lacking from the toxicology data. On the contrary, since 3,4-DAP SR did not contain much toxicology data, data were adopted from the IR formulation, like for Firdapse®. The genotoxicity data were conducted from studies with 3,4-DAP IR and given in the AR of Firdapse®. The lacking data about the single-dose toxicity of 3,4-DAP SR were obtained from literature[23]. The pharmaceutical company of Firdapse® conducted the reproduction toxicity study after approval; this toxicity study was a requirement of approval along with the carcinogenicity study (see supplementary 2).

The ecotoxicity/environmental risk assessment for both medicinal products was acquired from 3,4-DAP IR (see supplementary 2). The results of this study were presented in the AR of Firdapse®.

Clinical

Overall, the clinical data for both Firdapse® and 3,4-DAP SR also contained data adopted from 3,4-DAP IR. A pharmacokinetic study in healthy volunteers was conducted after approval of Firdapse® and published in 2014[24], see supplementary 3. At the time of approval, these data were not yet provided, thus the available data were similar to 3,4-DAP SR. Data about the pharmacokinetic interactions and pharmacokinetics using human biomaterials were not available for both products.

The presented pharmacodynamic data of 3,4-DAP SR were the same as Firdapse® (see supplementary 3). The primary pharmacology, the relation between plasma concentration and effect, and the pharmacodynamic interactions with other medicinal products or substances were acquired from 3,4-DAP IR for both products. For the clinical efficacy and safety almost all required data were available for both Firdapse® and 3,4-DAP SR, with the exception of data for special populations, such as patients with hepatic or renal impairment (see supplementary 3). Due to the long-term availability of 3,4-DAP SR, more experience in patients has been established compared to Firdapse®

Discussion

In this study, the AR of the licensed Firdapse® and the product dossier of the pharmaceutical preparation 3,4-DAP SR were analysed to investigate whether data fulfilled the requirements for marketing authorization as described by the EMA or which studies should be initiated to complete the lacking data. Since not all required data were available at the time of marketing authorization, due to the small LEMS patient cohort, Firdapse® was approved 'under exceptional circumstances'[7]. At the time of approval, most of the data were equally available for both Firdapse® and 3,4-DAP SR. Furthermore, most of the data used for the approval of Firdapse® originated from 3,4-DAP IR[10].

Firdapse®

Only two medium-sized bioequivalence studies (one in animals and one in healthy volunteers) and one small pharmacology safety study was performed with Firdapse® before applying for marketing authorization[7]. Due to the demonstrated bioequivalence studies, with equal areas under the curves (AUC) for both Firdapse® and 3,4-DAP IR, bridging of (non-) clinical data from 3,4-DAP IR was justified for Firdapse®. The equal AUCs support the assumption that efficacy between those two medicinal products is identical[25].

After marketing authorization approval, additional studies were required by the EMA. For non-clinical data, a carcinogenicity and a reproduction toxicity study still had to be performed. Furthermore, a clinical pharmacokinetic study, concerning the effects of food intake[26] and genetic variation in aryl N-acetyltransferase[24], was required. All required additional studies were

conducted, except for the non-clinical carcinogenicity study[7]. At last, more data about the clinical efficacy and safety had to be obtained, which was achieved by executing a phase III, randomised, double-blinded clinical trial[27], on the company's own initiative, and by the establishment of an LEMS patient registry in Europe[28]. With the patient registry, additional long-term efficacy and safety data is provided and the exposure to Firdapse® can be monitored[28]. Furthermore, this patient registry may collect additional data about special populations, such as patients with hepatic or renal impairment[7,28].

3,4-DAP SR

Many characteristics of 3,4-DAP SR originated from the IR, like Firdapse®. Data from 3,4-DAP IR can be used for the SR formulation, since both pharmaceutical formulations contain the same active ingredient, as shown in figure 2. It is also expected that the exposure is the same as 3,4-DAP IR (in case the active ingredient is completely absorbed)[25,29]. To confirm these assumptions, a pharmacokinetic study should be conducted to determine whether the AUC of 3,4-DAP SR equals the AUC of Firdapse®, and thus 3,4-DAP IR. By using the same study design as the pharmacokinetic study of Firdapse®[26], the results can be compared without using the expensive medicinal product in a study design. By using this strategy, no study is required that directly compares the pharmacokinetics of Firdapse® with 3,4-DAP SR. In case the AUC of 3,4-DAP SR equals the AUCs of the IR and Firdapse®, non-clinical data of Firdapse® can be used for 3,4-DAP SR as well.

3,4-DAP SR has been used for over 20 years in regular clinical care in The Netherlands, which means long-term experience in patients. Up to now, no severe, likely related adverse events have been reported at the Dutch pharmacovigilance database (Lareb) taking into account that no official pharmacovigilance has been performed yet.

Scoring of the availability of the aspects, "yes" or "no", in the AR or in the product dossier do not reflect the extensiveness of the available data. An extensive amount of the required data for marketing authorization was discussed in the AR of Firdapse®, but sometimes the data were only briefly described. Also for 3,4-DAP SR, not all the data are comprehensively described, for example, the quality part is not as extensively described as Firdapse®. Whereas parts of the guideline are very descriptive about the requirements of quality, non-clinical and clinical aspects of the marketing authorisation application, these requirements were not always met by Firdapse® (and 3,4-DAP SR). Still, our analysis provides a good overview of the data required for approval and which data can be collected after approval for 3,4-DAP SR.

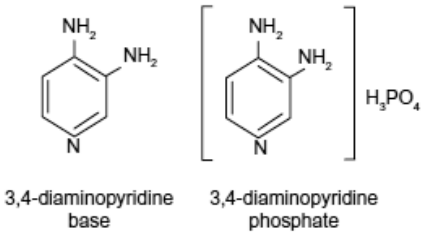

Figure 2. Chemical structures of 3,4-diaminopyridine base and 3,4-diaminopyridine phosphate (Firdapse®). Figure adapted from Lindquist, 2011[34]. Both 3,4-DAP base and 3,4-DAP phosphate (Firdapse®) contain the same active ingredient. 3,4-DAP = 3,4-diaminopyridine; SR = Slow release.

Furthermore, we have to keep in mind that the Firdapse® and 3,4-DAP SR is a specific case of a pharmaceutical preparation, and in order to apply for licensing a high level of documentation is needed. However, we think that this example clarifies the possibilities of pharmaceutical preparations towards licensing as a possibility to keep treatment available at reasonable costs.

Another possibility to avoid tremendous increases in pricing after licensing former pharmaceutical preparations can be established by more involvement from the government in protecting the purpose of the (ultra-) orphan drug designation. For example, in case the (ultra-)orphan medicinal product exceeds the number of 50 000 patients using it[4], the qualification of an (ultra-) orphan drug expires and the exclusivity period can be decreased[30]. In Japan, pharmaceutical companies pay a 1% sales tax on orphan drugs with annual profits exceeding 100 million Japanese yen (approximately €900 000,-)[30]. Moreover, the price transparency can be increased. In the EU, the pricing of (ultra-) orphan drugs is completely confidential which leads to unanswered questions[31].

Increased supervision of the Health Technology Assessment (HTA) might also positively influence the price tag[32]. The HTA should supervise the data on which a product received marketing authorization. In the case of a sudden and extreme price increase, without significant research performed by the pharmaceutical company to justify this increase in pricing, it is advisable that the HTA can impose restrictions to stop the tremendous price increase.

Since the available data from 3,4-DAP SR did not differ substantially from Firdapse® at the time of approval, there is a possibility that academic institutions can retrieve marketing authorization for pharmaceutical preparations after long-term use. As shown in the case of Firdapse®, a medicinal product can receive marketing authorization with hardly any original research and some small additional studies. However, in academic institutions, applying for marketing authorization is not a priority: since the focus is more science and care-driven instead of product-driven[33]. A commencement can be made by ensuring good documentation and quality controls to guarantee safety of the product for the patients. Subsequently, registration of all safety and efficacy data can

be obtained via good documentation, such as an LEMS patient registry, and can be used for applying for marketing authorization with such a product. Another possibility is to collaborate with a pharmaceutical company, to ensure safety for patients against affordable prices.

Conclusions

In conclusion, at time Firdapse® retrieved marketing authorization approval, the available data did not differ much from 3,4-DAP SR, indicating that marketing authorization approval with 3,4-DAP SR would have been possible, most likely 'Under Exceptional Circumstances'. Such approval requires post-marketing additional studies like it was the case for Firdapse®. To license 3,4-DAP SR, a pharmacokinetic study in healthy volunteers is necessary and investigation of long-term safety and efficacy could be established by collecting data in a patient registry. To avoid the tremendous price increases of pharmaceutical preparations like 3,4-DAP SR, the involvement of the government and HTA can lead to more control over the data used for marketing authorization by a commercial company. Furthermore, 3,4-DAP shows the possibility of retrieving marketing authorization with a pharmaceutical preparation by academic GMP licensed institutions.

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Supplementary 1

Table 1. Available data on quality aspects for Firdapse® and 3,4-diaminopyridine slow release (3,4-DAP SR)

Quality aspects	Firdapse® Data available (Yes/No)	3,4-DAP SR Data available (Yes/No)
Introduction	Yes	Yes
Active substance		
Active substance	Yes	Yes
Manufacture	Yes	Yes
Specification	Yes	Yes
Stability	Yes	Yes
Medicinal product		
Pharmaceutical development	Yes	Yes
Adventitious agents	Yes	Yes
Manufacture of the product	Yes	Yes
Product specification	Yes	Yes
Stability of the product	Yes	Yes
Discussion on chemical, pharmaceutical, and biological aspects	Yes	Yes

Supplementary 2

Table 1. Available data on non-clinical aspects for Firdapse® and 3,4-diaminopyridine slow release (3,4-DAP SR)

Non-clinical aspects		Firdapse® Data available (Yes/No)	3,4-DAP SR Data available (Yes/No)
Introduction		Yes	Yes
Pharmacology			
Primary pharmacodynamics	In vitro data	Yes [*1]	Yes [*1]
	In vivo data	Yes	Yes [*1]
Secondary pharmacodynamics		Yes [*1]	Yes [*1]
Safety pharmacology programme		Yes	No
Pharmacodynamic drug interactions		No	No
Pharmacokinetics			
Absorption		Yes	Yes [*1]
Distribution		Yes	No
Metabolism		No	No
Excretion		No	No
Pharmacokinetic drug interactions		No	No
Toxicology			
Single-dose toxicity		Yes	Yes [*1]
Repeat-dose toxicity		Yes	No
Genotoxicity		Yes [*1]	Yes [*1]
Carcinogenicity		No	No
Reproduction toxicity		Yes [*2]	No
Toxicokinetic data		Yes	No
Local tolerance		NA	NA
Other toxicity studies		Yes	Yes [*1]
Ecotoxicity/environmental risk assessment		Yes [*1]	Yes [*1]
Discussion on the non-clinical aspects		Yes	Yes

*[1] Data from 3,4-DAP immediate release; *[2] Data obtained after approval of Firdapse®

Supplementary 3

Table 1. Available data on clinical aspects for Firdapse® and 3,4-diaminopyridine slow release (3,4-DAP SR)

Clinical aspects		Firdapse®	3,4-DAP SR
		Data available (Yes/No)	Data available (Yes/No)
Introduction		Yes	Yes
GCP		Yes	Yes
Pharmacokinetics			
Absorption	Bioequivalence	Yes	Yes[*1]
	Bioavailability	Yes[*2]	No
Distribution and elimination	Metabolism	Yes[*2]	No
	Dose proportionality and time dependencies	Yes[*2]	No
	Intra- and inter-individual variability	Yes[*2]	No
	Special populations	Yes[*2]	No
	Pharmacokinetic interaction studies	No	No
	Pharmacokinetics using human biomaterials	No	No
Discussion on pharmacokinetics		Yes	Yes
Pharmacodynamics			
Mechanism of action		Yes	Yes
Pharmacology	Primary pharmacology	Yes[*1]	Yes[*1]
	Secondary pharmacology	No	No
	Relation between plasma concentration and effect	Yes[*1]	Yes[*1]
	Pharmacodynamic interactions with other medicinal products or substances	Yes[*1]	Yes[*1]
Discussion on pharmacodynamics		Yes	Yes
Clinical efficacy	Clinical efficacy	Yes[*1,3]	Yes[*1]
	Clinical studies in special populations	No	No
	Supportive studies	Yes[*1]	Yes[*1]
Discussion on clinical efficacy		Yes	Yes
Clinical safety	Patient exposure	Yes[*1,3]	Yes[*1,3]
	Adverse events	Yes[*1,3]	Yes[*1,3]
	Serious adverse event/deaths/other significant events	Yes[*1,3]	Yes[*1,3]
	Laboratory findings	Yes[*1]	Yes[*1]
	Safety in special populations	No	No
	Safety related to drug-drug interactions and other interactions	Yes[*1]	Yes[*1]
	Discontinuation due to adverse events	Yes[*1,3]	Yes[*1,3]
	Post-marketing experience	Yes	Yes
Discussion on clinical safety		Yes	Yes

[*1] Data from 3,4-DAP IR; [*2] Data obtained after approval of Firdapse®; [*3] limited data about the medicinal product itself.