Considerations for clinical development of intravenous formulations containing the same active ingredient as oral products for patients who are temporarily unable to receive oral administration in epilepsy treatment
（Early consideration）

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1. Introduction

Epilepsy is a chronic disease characterized by repetitive paroxysmal symptoms of the brain, and epileptic seizures are thought to be caused by excessive excitation of nerve cells in the cerebrum[1)]. To date, multiple epilepsy treatments have been approved in Japan; however, abrupt discontinuation of antiepileptic drugs raises concerns about seizure recurrence and status epilepticus, and gradual tapering is the principle even when discontinuing treatment1). Therefore, when oral administration is temporarily difficult, it is considered desirable to administer the antiepileptic drug being used or an alternative intravenously[2, 3)].

The purpose of this document is to present basic considerations for clinical development of intravenous formulations containing the same active ingredient as oral formulations for patients who are temporarily unable to receive oral administration in epilepsy treatment. It should be noted that these considerations are based on currently available knowledge and may change as new findings emerge.

2. Considerations for Clinical Studies

2.1 General Issues

For the development of intravenous formulations as an alternative when oral administration is temporarily not possible in epilepsy treatment, it is a prerequisite that the efficacy and safety have been confirmed in clinical studies of the oral formulation in epilepsy patients. Furthermore, in the development of intravenous formulations, appropriate evaluation should be ensured after considering the following points.

- It is necessary to confirm that the pharmacokinetic profiles of oral and intravenous formulations are similar.
- Considering that C_{max} is thought to be higher with intravenous administration compared to oral administration, the appropriateness of the dose and infusion rate of the intravenous formulation, as well as the similarity in safety and efficacy between oral and intravenous formulations, should be confirmed. Both cases of switching from the oral formulation to the intravenous formulation and administering the intravenous formulation prior to the oral formulation need to be examined.
- For the evaluation of efficacy and safety of intravenous formulations, when similar pharmacokinetics between oral and intravenous formulations are demonstrated and pharmacokinetic changes before and after switching are clinically judged to have ""no impact,"" it is not necessarily required to plan and conduct randomized double-blind comparative studies for the clinical development of intravenous

formulations with the same active ingredient as approved oral formulations. For example, comparing the change in seizure frequency before and after switching from oral to intravenous formulations and examining the occurrence of adverse events is one option.

- In switching studies from oral to intravenous formulations, switching to the intravenous formulation should occur after the oral formulation has been administered for a certain period.

2.2 Pharmacokinetics analysis

Pharmacokinetic analysis should be designed according to the objectives of the clinical study. To avoid arbitrary interpretation of the obtained results, analytical methods and success criteria should be specified in advance.

In analyzing pharmacokinetics, using population pharmacokinetic models may be considered as one possible approach.

2.3 Efficacy Endpoints

For evaluating efficacy, it is appropriate to set clinical endpoints such as seizure frequency over a certain period. From the perspective of comparing oral and intravenous formulations, it is desirable to use the efficacy endpoints used in confirmatory studies of the oral formulation.

To avoid arbitrary interpretation of the obtained results, success criteria should also be specified in advance.

While the use of surrogate markers (e.g., changes in EEG findings) as efficacy endpoints can be considered, it is currently difficult to evaluate the efficacy of intravenous formulations based solely on the results of surrogate markers.

2.4 Study population

The study population for clinical studies to evaluate the efficacy and safety of intravenous formulations should be within the indication range of the oral formulation. When the oral formulation has multiple indications (e.g., partial seizures and tonic-clonic seizures), in principle, the efficacy and safety of the intravenous formulation should be evaluated for patients with each indicated disease. However, when conducting clinical studies using the intravenous formulation in patients with specific indications is difficult from the perspective of clinical trial feasibility, it may be acceptable not to conduct clinical studies using the intravenous formulation in patients with those indications provided that the rationale for expected efficacy of the intravenous formulation is scientifically confirmed based on pharmacokinetic similarities or differences among patients with indicated diseases and clinical study results of the oral formulation.

2.5 Treatment period

The evaluation period in clinical studies should be established considering the administration period of the intravenous formulation and the study design with specified endpoints. However, when efficacy and safety have been confirmed with the oral formulation and similarity between oral and intravenous formulations has been demonstrated in pharmacokinetic studies, short-term evaluation may be acceptable.

3. Drug development in pediatric population

The basic approach for development in pediatric populations is the same as for adults. For pediatric patients with specific indications, the development strategy should be examined considering whether extrapolation of study results from other populations such as adult patients is possible from the perspective of clinical trial feasibility. When extrapolating clinical study results from other populations, consideration should be given to the "Clinical Investigation of Medicinal Products in the Pediatric Population" (ICH E11) and its addendum[4, 5]. The clinical data required by the time of approval application need to be considered on a case-by-case basis for each product. Therefore, it is recommended to utilize PMDA's clinical trial consultations from the early stages of planning clinical studies for intravenous formulations.

4. References

1) てんかん診療ガイドライン 2018. 医学書院; 2018
2) CNS drugs 2015; 29: 1009-22
3) Curr Pharm Des 2017; 23: 6524-32
4) “Clinical Investigation of Medicinal Products in the Pediatric Population” (PMSB/ELD Notification No. 1334 dated December 15, 2000)
5) “Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population” (PSEHB/ELD Notification No. 1227-5 dated December 27, 2017)

以上