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Pharmaceuticals and Medical Devices Agency

Office of New Drug III

EARLY CONSIDERATION:

Points to Consider for the Design of Clinical Trials to Assess the Effects of Psychotropic Drugs on Driving Performance

1. Background

Recent psychotropic drugs¹⁾ have been shown to reduce sedative side effects making them more tolerable. Therefore, examining the effects of psychotropic drugs on driving performance and providing appropriate precautions regarding their effects on patients will not only protect patient safety but also contribute to improving opportunities to provide appropriate therapeutic drugs. To facilitate the efficient and appropriate evaluation of the effects of psychotropic drugs on driving performance, the Ministry of Health, Labour and Welfare (MHLW) of Japan has issued and implemented the guideline for evaluating the effects of psychotropic drugs on motor vehicle driving performance^{2,3)}. As the MHLW guideline recommends the use of a tiered approach, it is appropriate to evaluate the profile of the investigational drug in a step-by-step manner and to identify the proposed studies needed, rather than conducting all the studies (including driving studies) indicated in the guideline. In addition, the MHLW guideline recommends that the profile of adverse events affecting driving should be evaluated appropriately in exploratory, validation and long-term studies.

Specifically, this document addresses important aspects of the design of clinical trials to assess the effects of psychotropic drugs on driving performance.

It should be noted that the consideration in this document is based on scientific evidence and international trends as of August 2024 and may change in the future due to these changes.

2. Points to consider for the design of clinical trials

Among sedative side effects, those affecting alertness, such as drowsiness caused by psychotropic drugs on driving performance, are more frequently observed during initial treatment stages and dose escalation. Hence, it becomes crucial to assess whether these side effects have clinically meaningful effects and the persistence of these effects, i.e. the ***“persistence of clinically meaningful impairment.”***

To assess the "persistence of clinically meaningful impairment," it is recommended that

the blood concentration of the investigational drug and its active metabolite and the temporal relationship of “adverse events affecting driving” be examined. Adverse events affecting driving are defined based on the pharmacological and other characteristics of the investigational drug. The temporal relationship includes the time of onset, duration, and tolerance. If the accumulated information from non-clinical and clinical studies suggests an effect on driving performance and driving studies are conducted, it is important to assess the magnitude and persistence of the effect. For specific analytical methods of “persistence of clinically meaningful impairment,” a recent review article⁴⁾ is helpful.

- 1) Psychotropic drugs are not psychotropic drugs as defined in the Narcotic Drugs and Psychotropic Substances Control Act in Japan, but rather drugs classified in the Japan Standard Commodity Classification (classification number) as, hypnotics and sedatives, antianxiotics (112), antiepileptics (113), psychotropic agents (117) and other agents affecting central nervous system including drugs for the treatment of insomnia, narcolepsy, and attention-deficit/hyperactivity disorder (119).
- 2) Ministry of Health, Labour and Welfare. Guideline for evaluating the effect of psychotropic drugs on the performance to drive a motor vehicle [in Japanese]. PSEHB/PED Notification No. 1227-3 and PSEHB/PSD Notification No. 1227-1., 2022.
- 3) Iwamoto K, Nakabayashi T, Yamaguchi A, Konishi Y, Saji M, Yoshimura R, Kanemoto K, Aoki H, Ando M, Ozaki N: The new guideline for evaluating effects of psychotropic drugs on the performance to drive a motor vehicle in Japan: Comparison with US FDA guideline. *Neuropsychopharmacol Rep.* 2023 Jun; 43(2): 172-176. doi: 10.1002/npr2.12339
- 4) Nakabayashi T, Iwamoto K, Yamaguchi A, Konishi Y, Saji M, Yoshimura R, Kanemoto K, Aoki H, Ando M, Ozaki N. Guideline for evaluating the effects of psychotropic drugs on motor vehicle driving performance in Japan: A tiered approach for the assessment of clinically meaningful driving impairment. *Neuropsychopharmacol Rep.* 2024 Jun; 44(2): 308-313. doi: 10.1002/npr2.12436.