This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

PSB/PED Notification No. 1021-5
PSB/PSD Notification No. 1021-3
October 21, 2026

To: Directors of Health Department (Bureau) of each [Prefecture / City with public health center / Special ward]

Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)
Director of Pharmaceutical Safety Division, Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Considerations for the Use of Avacopan Products

Regarding the identification of concerns in the reliability of the results from the multi-regional clinical trial used in the approval review for avacopan (brand name: Tavneos Capsules 10 mg; hereinafter referred to as "the drug"), a written order to report was issued to Kissei Pharmaceutical Co., Ltd. (hereinafter referred to as "the marketing authorization holder") on June 19, 2026 pursuant to the provisions of Article 69, Paragraph 6 and Article 69-2, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960; hereinafter referred to as the "Pharmaceuticals and Medical Devices Act") and has requested the submission of a written response.

The Pharmaceuticals and Medical Devices Agency (PMDA) reviewed the contents of the response submitted by the marketing authorization holder in accordance with the order to report and confirmed that there could be issues regarding the reliability of the data submitted for the approval review. As a result, it could not conclude that the therapeutic benefits of the drug outweigh the risks. Consequently, it was reported as attached, to the Second Committee on Drugs of the Pharmaceutical Affairs Council during a meeting held on October 21, 2026.

Please inform medical institutions under your jurisdiction of the following matters as specific points to consider when using the drug.

A copy of this notification has also been issued to the heads of the relevant organizations specified in the Note.

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<Specific points to consider when using the drug >

1. Initiation of treatment with the drug should be withheld in new patients.
2. For patients currently receiving the drug, discontinuation of the treatment or switching to an alternative treatment should, in principle, be considered. Discontinuation or switching to an alternative treatment should be considered based on each patient's disease condition, treatment response, other treatment options, and the impact of changing the treatment.
3. Where the use of the drug is continued, including the period prior to switching to an alternative treatment, appropriate use should be maintained in accordance with the Dear Healthcare Professionals Letter of Rapid Safety Communication (BLUE LETTER) issued on May 21, 2026.

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Note

President of Japan Medical Association
President of Japan Pharmaceutical Association
President of Japanese Society of Hospital Pharmacists
President of Japan College of Rheumatology
President of Japanese Society of Nephrology

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Attachment

Action regarding Tavneos Capsules 10 mg

October 21, 2026
Pharmaceutical Safety Bureau

1. Outline of the product

- Tavneos Capsules 10 mg (Nonproprietary name: avacopan; hereinafter referred to as "the drug") is an orphan drug for which Kissei Pharmaceutical Co., Ltd. (hereinafter referred to as "the marketing authorization holder") filed an approval application for the indications of microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). After being reviewed by the Second Committee on Drugs on September 6, 2021, the drug was approved on September 27, 2021.
- The pivotal evidence for the approval application of the drug was the results of the CL010_168 Study (hereinafter referred to as "ADVOCATE Study"), a global phase III clinical trial conducted by the sponsor ChemoCentryx, Inc. of the U.S. (hereinafter referred to as the "U.S. sponsor").
- Alerts regarding serious hepatic dysfunction with the drug have been communicated since the time of approval. Among cases of serious hepatic dysfunction including fatal cases that have been accumulated since the market launch in June 2022, cases for which a causal relationship with the drug could not be ruled out were identified. Therefore, in May 2026, a Dear Healthcare Professionals Letter of Rapid Safety Communication (BLUE LETTER) was issued to call attention to promote early detection of hepatic dysfunction and prevent progression to severe outcomes.

2. Current situation concerning the drug

- The regulatory authorities in Europe and the U.S. have raised concerns regarding the reliability of the results of the ADVOCATE study, and regulatory actions are being taken (* 1).

  * 1: In Europe, the approval was withdrawn in August 2026.
  The U.K. terminated the use of the drug for new patients in September 2026, and plans to withdraw the approval of the drug on March 1, 2027, providing a 6-month transition period for patients currently receiving the drug.
  In the U.S., the withdrawal of the approval was proposed in April 2026, and a procedure for hearing from the company is ongoing.

- In Japan, an order to report was issued to the marketing authorization holder on June 19, 2026 pursuant to Article 69, Paragraph 6 and Article 69-2, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, and a written response in accordance with the order to report was submitted on July 21. The PMDA reviewed the response, issued additional inquiries to the marketing authorization holder and submitted a report to the Ministry on October 19.

3. Matters related to the reliability of the study results

- At present, the PMDA's report on the responses from the marketing authorization holder concerning the reliability of the ADVOCATE study is as follows.
  - In the analysis after the initial database lock, superiority of the drug group over the control group was not demonstrated in terms of remission maintenance rate at Week 52, which was the primary endpoint.
  - Unblinded personnel, who knew the analysis results after the initial database lock and the treatment assignment of each subject, identified 9 subjects as candidates for re-adjudication of the primary endpoint.
  - When the independent review committee (* 2) was asked to re-adjudicate the 9 subjects, it was not explained that the superiority had not been demonstrated in the initial analysis. In addition, the committee did not receive any explanation of the process by which the unblinded personnel identified the 9 subjects for re-adjudication and that an analysis assuming changes in the adjudication results had been performed.

    * 2: An external panel of experts that determines the treatment response in each patient based on predefined criteria while being blinded to the treatment
  - A reanalysis was performed using the data incorporating the re-adjudication results, and the results of the reanalysis were described as the final analysis results in the approval application materials.
  - In the approval application materials, the results of the initial analysis, the process of identifying the candidate subjects for re-adjudication in which the unblinded personnel was involved, the analysis assuming changes in the adjudication results, and a series of processes leading to the request for re-adjudication to the independent review committee were not appropriately described.

- In the compliance inspection conducted by the PMDA in June 2021 at the time of approval review, the marketing authorization holder and the U.S. sponsor who attended the inspection together with the marketing authorization holder explained that a series of re-adjudication related to this matter was performed in accordance with a certain procedure, subjects requiring re-adjudication were identified in accordance with a certain procedure to ensure the accuracy of the data, and the blinding of personnel involved in the study had been maintained.

4. Matters concerning the efficacy and safety of the drug

- The PMDA has reported regarding the responses from the marketing authorization holder concerning efficacy and safety of the drug as follows.
  - The results of the ADVOCATE Study do not conform to the reliability standard applicable to approval application materials, and therefore it is inappropriate to use the results of this study as evidence supporting the efficacy of the drug. Furthermore, it cannot be concluded that the efficacy of the drug has been verified based on information obtained after marketing.

- Regarding safety, it is considered unnecessary to take additional safety measures for the use of the drug at this stage for the following reasons:
  - Although careful attention should be paid to hepatic dysfunction, safety measures such as the issuance of a Dear Healthcare Professionals Letter of Rapid Safety Communication and revision of the package insert have been taken, and no clear increasing trend in reported cases has been observed, suggesting that the safety measures implemented to date have had a certain effect. Therefore, the impact of these measures will be evaluated while information, such as adverse reaction reports, is further collected.
  - With respect to serious infections and other adverse reactions, no obvious difference from the safety profile identified by the time of marketing approval has been observed.
- Based on the above, hepatic dysfunction remains a safety concern that requires focused evaluation. Meanwhile, as information establishing the efficacy of the drug has not been obtained at this point, it cannot be concluded that the therapeutic benefits of the drug outweigh the risks.

5. Current action policy

- Based on 3. and 4., it was confirmed that there could be issues regarding the reliability of the data submitted at the time of approval application, and was reported that it cannot be concluded that the therapeutic benefits of the drug outweigh the risks. Therefore, it is necessary to take measures for the time being from the perspective of patient protection.
- On the other hand, the diseases for which the drug is indicated are serious rare diseases, and it is considered necessary to make decisions regarding treatment changes on an individual basis, taking into account each patient's disease condition and other treatment options.
- Based on the above, medical institutions and other relevant organizations will be requested to take the following actions with regard to administration of the drug for the time being (see Attachment (omitted)).
  1. **Initiation of treatment with the drug should be withheld in new patients.**
  2. **For patients currently receiving the drug, discontinuation of the treatment or switching to an alternative treatment should, in principle, be considered. Discontinuation or switching to an alternative treatment should be considered based on each patient's disease condition, treatment response, other treatment options, and the impact of changing the treatment.**
  3. **Where the use of the drug is continued, including the period prior to switching to an alternative treatment, appropriate use should be maintained in accordance with the Dear Healthcare Professionals Letter of Rapid Safety Communication (BLUE LETTER) issued on May 21, 2026.**