



NDA 214121/S-006

SUPPLEMENT APPROVAL

Accord Healthcare Inc.
Attention: Sabita Nair, RAC, ASQ-CPGP
Vice President, Regulatory Affairs
8041 Arco Corporate Drive, Suite 200
Raleigh, NC 27617

Dear Sabita Nair:

Please refer to your supplemental new drug application (sNDA) dated and received July 15, 2026, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methotrexate Injection USP, 100 mg/mL, 50 mL.

We also refer to our letter dated July 9, 2026, notifying you, under Section 505(o)(4) of the FD&C Act, of new safety information that we have determined should be included in the labeling for intravenous methotrexate products. This information pertains to the serious risk of a drug-drug interaction when intravenous methotrexate is used concomitantly with dasatinib or imatinib, resulting in increased plasma concentrations of methotrexate that may increase risk of serious adverse reactions.

This supplemental new drug application provides for revisions to the labeling for methotrexate. The agreed upon changes to the language included in our July 9, 2026, letter are as follows (additions are noted by underline and deletion are noted by ~~striketrough~~).

1. Section 7.1, Effects of Other Drugs on Methotrexate

Coadministration of methotrexate with the following products may increase methotrexate plasma concentrations, which may increase the risk of severe adverse reactions to methotrexate.

- Penicillin or sulfonamide antibiotics
- Highly protein bound drugs (e.g., oral anticoagulants, phenytoin, salicylates, sulfonamides, sulfonyleureas, and tetracyclines)
- Proton pump inhibitors
- Probenecid
- Antifolate drugs (e.g., dapsone, pemetrexed, pyrimethamine and sulfonamides)
- Aspirin and other nonsteroidal anti-inflammatory drugs

Unexpectedly severe and fatal gastrointestinal toxicity can occur with concomitant administration of methotrexate (primarily at high dose) and nonsteroidal anti-inflammatory drugs (NSAIDs).

- Mercaptopurine
- Weak acids (e.g., salicylates)
- Hematotoxic agents
- Imatinib
- Dasatinib

2. Section 12.3, Pharmacokinetics

Drug Interaction Studies

In Vitro Studies

Transporter Systems: Methotrexate is a substrate of BCRP, MRP1, MRP2, MRP3, MRP4, OATP1B1, OATP1B3, OAT1, and OAT3, ~~MATE1 and MATE2/k.~~

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling minor editorial revisions listed below and reflected in the enclosed labeling.

- The revised date was updated to 10/2026

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.³ Information and Instructions for completing the form can be found at FDA.gov.⁴

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

³ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Emily Pak, Safety Regulatory Project Manager, at 301-837-7531, or via email at Emily.Pak@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shan M. Pradhan, M.D.
Associate Director for Safety
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
 - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHAN PRADHAN
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