DOCUMENT INFORMATION PAGE

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Application #(s):	NDA 220201
Communication Type:	Correspondence
Communication Group:	NDA Action
Communication Name:	Approval
Communication ID:	COR-NDAACTION-03
Drafted by:	K.Jarrell 01.25.26;
Clearance History:	A. Zack-Taylor 01/26/26; N.Griffin: 2.9.2026
Finalized:	S.Lemery02.17.26
Filename:	Approval_N220201
Signatory Authority:	NMEs must be signed by the Office Director or Deputy Office Director. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Used to issue an Approval letter to original NDAs, effective on date of letter.
Notes:	USE FOR **PRESCRIPTION** APPROVALS ONLY **Note:** Remember to check for acceptability of facility **prior to issuing approval letter**. For controlled substances where DEA scheduling is not complete: Remember to set the '505(x) property' for the application/project in the electronic archive system **prior to issuing approval letter**. **Labeling:** Before attaching labeling, ensure that the following items have been addressed (see "Final Check of Labeling Format Before Attaching Documents to Approval Letter" slide presentation on *CDER Prescription Drug Labeling Resources website* for details): 1) Remove annotations (e.g., tracked changes, comments, content in headers/footers); however, page numbers are allowed (see #5) 2) Remove line numbers

3) Assess number of columns in three sections of labeling (two columns for Highlights and Table of Contents, and one-column for Full Prescribing Information). If incorrect, ask applicant to address.
4) Correct/update dates in Highlights (e.g., Initial U.S. Approval, Recent Major Changes, and Revision Date)
5) If page numbers are included, ensure first page of each labeling document starts with Page #1 (e.g. Prescribing Information, Patient Package Insert, Medication Guide, and Instructions for Use all start with Page #1)

Version: 02/25/2025

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

NDA 220201

NDA APPROVAL

Avyxa Holdings, LLC
Attention: Mukteeshwar Gande, M.S., R.Ph.
Chief Scientific Officer
RiconPharma LLC (Agent for Avyxa Holdings, LLC)
100 Ford Road, Suite #9
Denville, NJ 07834

Dear Mukteeshwar Gande:

Please refer to your new drug application (NDA) received April 23, 2025, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Favlyxa, (fluorouracil) injection.

This NDA provides for the use of Favlyxa (fluorouracil) injection for the following indications:

- Adenocarcinoma of the Colon and Rectum
- Adenocarcinoma of the Breast
- Gastric Adenocarcinoma
- Pancreatic Adenocarcinoma

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.

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) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[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.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your December 17, 2025, submission containing draft carton and container labeling.

Submit final printed carton and container labeling that are identical to the December 17, 2025, submitted carton and container labeling. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 220201."** Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Favlyxa, Fluorouracil Injection USP, 250 mg/10 mL (25 mg/mL), shall be 18 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F) [USP Controlled Room Temperature].

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 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 the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

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

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[6].

If you have any questions, contact Kristin Jarrell, Pharm.D, Regulatory Project Manager, at (301) 796-0137.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] https://www.uspnf.com/

Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FAVLYXA safely and effectively. See full prescribing information for FAVLYXA.

FAVLYXA™ (fluorouracil) injection, for intravenous use
Initial U.S. Approval: 1962

WARNING: SERIOUS ADVERSE REACTIONS OR DEATH IN PATIENTS WITH COMPLETE DPD DEFICIENCY

- **Increased risk of serious adverse reactions or death in patients with complete DPD deficiency.**
- **Test patients for genetic variants of DPYD prior to initiating FAVLYXA unless immediate treatment is necessary. Avoid use of FAVLYXA in patients with certain homozygous or compound heterozygous DPYD variants that result in complete DPD deficiency. (5.1)**

----------INDICATIONS AND USAGE----------
FAVLYXA is a nucleoside metabolic inhibitor indicated for the treatment of patients with:
- Adenocarcinoma of the Colon and Rectum (1.1)
- Adenocarcinoma of the Breast (1.2)
- Gastric Adenocarcinoma (1.3)
- Pancreatic Adenocarcinoma (1.4)

----------DOSAGE AND ADMINISTRATION----------
- FAVLYXA is recommended for administration either as an intravenous bolus or as an intravenous infusion. (2.1)
- Adenocarcinoma of the Colon and Rectum
  - In combination with leucovorin or as a component of a multidrug chemotherapy regimen that includes leucovorin (infusional regimen): 400 mg/m^2 for one dose, followed by 2,400 mg/m^2 to 3,000 mg/m^2 over 46 hours on day 1 of each 2-week cycle or
  - In combination with leucovorin (bolus regimen): 500 mg/m^2 on days 1, 8, 15, 22, 29 and 36 of each 8-week cycle. (2.2)
- Adenocarcinoma of the Breast in combination with a cyclophosphamide-based multidrug regimen: 500 mg/m^2 or 600 mg/m^2 on days 1 and 8 of each 28-day cycle (bolus regimen). (2.2)
- Gastric Adenocarcinoma in combination with a platinum-containing multidrug regimen: 200 mg/m^2 to 1,000 mg/m^2 over 24 hours (infusional regimen). (2.2)
- Pancreatic Adenocarcinoma in combination with leucovorin or as a component of a multidrug chemotherapy regimen that includes leucovorin: 400 mg/m^2 on day 1, followed by 2,400 mg/m^2 over 46 hours every 2 weeks (infusional regimen). (2.2)
- Refer to Section 2.3 for dosage modifications due to adverse reactions.

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 250 mg/10 mL (25 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Cardiotoxicity: FAVLYXA can cause cardiotoxicity, including angina, myocardial infarction/ischemia, arrhythmia, and heart failure. Withhold FAVLYXA for cardiac toxicity. (5.2)
- Hyperammonemic Encephalopathy: Altered mental status, confusion, disorientation, coma, or ataxia with elevated serum ammonia level can occur within 72 hours of initiation of FAVLYXA. Withhold FAVLYXA and initiate ammonia-lowering therapy. (5.3)
- Neurologic Toxicity: FAVLYXA can cause acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances. Withhold FAVLYXA for neurologic toxicity. (5.4)
- Diarrhea: FAVLYXA can cause severe diarrhea. Withhold FAVLYXA for severe diarrhea until resolved. (5.5)
- Palmar-Plantar Erythrodysesthesia Syndrome: Based on severity, withhold FAVLYXA until resolved or decreased to Grade 1, then resume at a reduced dose. (5.6)
- Myelosuppression: FAVLYXA can cause severe and fatal myelosuppression. Withhold FAVLYXA until severe myelosuppression resolves, then resume at a reduced dose. (5.7)
- Mucositis: FAVLYXA can cause severe mucositis. Withhold FAVLYXA until resolved or decreased to Grade 1, then resume at a reduced dose. (5.8)
- Increased Risk of Bleeding with Concomitant Use of Warfarin: Concurrent administration with warfarin can result in clinically significant increases in coagulation parameters: Closely monitor INR and prothrombin time. (5.9)
- Embryofetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)

----------ADVERSE REACTIONS----------
To report SUSPECTED ADVERSE REACTIONS, contact Avyxa Pharma, LLC at 1-888-520-0954 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed (8.2)
- Infertility: May impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS ADVERSE REACTIONS OR DEATH IN PATIENTS WITH COMPLETE DPD DEFICIENCY

- **Increased risk of serious adverse reactions or death in patients with complete DPD deficiency.**
- **Test patients for genetic variants of *DPYD* prior to initiating FAVLYXA unless immediate treatment is necessary. Avoid use of FAVLYXA in patients with certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

FAVLYXA is indicated for the treatment of patients with:

1.1 Adenocarcinoma of the Colon and Rectum
1.2 Adenocarcinoma of the Breast
1.3 Gastric Adenocarcinoma
1.4 Pancreatic Adenocarcinoma

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation and Testing for DPD Deficiency Before Initiating FAVLYXA

Prior to initiating FAVLYXA, test patients for genetic variants of the *DPYD* gene unless immediate treatment is necessary. An FDA-authorized test for the detection of the *DPYD* gene to identify patients at risk of serious adverse reactions with FAVLYXA is not currently available. Currently available tests used to identify *DPYD* variants may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).

Avoid use of FAVLYXA in patients known to have certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency. No FAVLYXA dose has been proven safe for patients with complete DPD deficiency. For patients with partial DPD deficiency, individualize the dosage and modify based on tolerability and intent of treatment *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

FAVLYXA is recommended for administration either as an intravenous bolus or as an intravenous infusion. Dosage recommendations are in Table 1.

Table 1: Recommended dosage of FAVLYXA

Indication	Recommended Dosage	Duration of Treatment
Adenocarcinoma of the Colon and Rectum		
In combination with leucovorin or as a component of a multidrug chemotherapy regimen that includes leucovorin	400 mg/m^2 for one dose, followed by 2,400 mg/m^2 to 3,000 mg/m^2 over 46 hours on day 1 of each 2-week cycle	Until disease progression or unacceptable toxicity.
In combination with leucovorin alone (bolus regimen)	500 mg/m^2 on days 1, 8, 15, 22, 29 and 36 of each 8-week cycle	Until disease progression or unacceptable toxicity.
Adenocarcinoma of the Breast		
In combination with cyclophosphamide-based multidrug regimen (bolus regimen)	500 mg/m^2 or 600 mg/m^2 on days 1 and 8 of each 28-day cycle	Until disease progression or unacceptable toxicity or 6 cycles
Gastric Adenocarcinoma		
In combination with a platinum-containing multidrug regimen	200 mg/m^2 to 1,000 mg/m^2 over 24 hours	Frequency in each cycle and length of each cycle depend on dose of FAVLYXA and specific regimen
Pancreatic Adenocarcinoma		
In combination with leucovorin or as a component of a multidrug chemotherapy regimen that includes leucovorin	400 mg/m^2 on day 1, followed by 2,400 mg/m^2 over 46 hours every 2 weeks	Until disease progression or unacceptable toxicity.

2.3 Dosage Modifications for Adverse Reactions

Withhold FAVLYXA for the following adverse reactions. Depending on the severity of the adverse reaction, either discontinue or resume FAVLYXA at a reduced dosage upon resolution or improvement to Grade 1:

- Grade 3 or 4 diarrhea *[see Warnings and Precautions (5.5)]*
- Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome) *[see Warnings and Precautions (5.6)]*
- Grade 3 or 4 mucositis *[see Warnings and Precautions (5.8)]*
- Grade 4 myelosuppression *[see Warnings and Precautions (5.7)]*

There is no recommended dose for resumption of FAVLYXA administration following development of any of the following adverse reactions; consider permanent discontinuation of FAVLYXA following:

- Development of angina, myocardial infarction/ischemia, arrhythmia, or heart failure in patients with no history of coronary artery disease or myocardial dysfunction *[see Warnings and Precautions (5.2)]*
- Hyperammonemic encephalopathy *[see Warnings and Precautions (5.3)]*
- Neurologic toxicity including acute cerebellar syndrome *[see Warnings and Precautions (5.4)]*

2.4 Preparation and Administration

FAVLYXA is a hazardous drug. Follow applicable special handling and disposal procedures[1].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For Direct Intravenous Bolus Injection

Preparation
- Select the appropriate number of vial(s) based on the prescribed dose.
- Withdraw the calculated dose into a sterile syringe.
- Discard partially used or empty vials of FAVLYXA.

Administration
- Administer FAVLYXA as an intravenous bolus through an established intravenous line over 2 to 5 minutes.
- Do not administer in the same intravenous line concomitantly with other medicinal products.

Storage
- If the dose is not administered, attach a tip cap to the syringe prior to storage. The syringe can be stored at room temperature 20°C to 25°C (68°F to 77°F) for up to 4 hours.

For Intravenous Infusion

Preparation
- Select the appropriate number of vial(s) based on the prescribed dose.
- Withdraw the calculated dose into a sterile syringe.
- Dilute the calculated dose in an appropriate amount of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, to prepare an infusion solution with a final concentration ranging from 1.5 mg/mL to 10 mg/mL.

Administration
- Do not administer in the same intravenous line concomitantly with other medicinal products.
- For intravenous infusion regimens, administer through a central venous line using an infusion pump.

Storage
- If not used immediately, the diluted FAVLYXA can be stored at room temperature 20°C to 25°C (68°F to 77°F) for up to 24 hours.

3 DOSAGE FORMS AND STRENGTHS

Injection: FAVLYXA contains 250 mg/10 mL (25 mg/mL) fluorouracil as colorless to light yellow clear solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Adverse Reactions or Death from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Patients with certain homozygous or compound heterozygous variants in the *DPYD* gene known to result in complete or near complete absence of DPD activity (complete DPD deficiency) are at increased risk for acute early-onset toxicity and serious, including fatal adverse reactions due to FAVLYXA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity (partial DPD deficiency) may also have increased risk of serious or fatal adverse reactions.

Prior to initiating FAVLYXA, test patients for genetic variants of the *DPYD* gene unless immediate treatment is necessary *[see Clinical Pharmacology (12.5)]*. Serious adverse reactions may still occur even if no *DPYD* variants are identified.

Avoid use of FAVLYXA in patients with certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency.

Withhold or permanently discontinue FAVLYXA based on clinical assessment of the onset, duration, and severity of adverse events in patients with evidence of acute early-onset or unusually severe reactions. No fluorouracil dose has been proven safe for patients with complete DPD deficiency. For patients with partial DPD deficiency, individualize the dosage and modify based on tolerability and intent of treatment.

An FDA-authorized test for the detection of genetic variants of the *DPYD* gene to identify patients at risk of serious adverse reactions with FAVLYXA treatment is not currently available. Currently available tests used to identify *DPYD* variants may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).

5.2 Cardiotoxicity

FAVLYXA can cause cardiotoxicity, including angina, myocardial infarction/ischemia, arrhythmia, and heart failure, based on postmarketing reports. Reported risk factors for cardiotoxicity are administration by continuous infusion rather than intravenous bolus and presence of coronary artery disease. Withhold FAVLYXA for cardiotoxicity. The risks of resumption of FAVLYXA in patients with cardiotoxicity that has resolved have not been established *[see Dosage and Administration (2.3)]*.

5.3 Hyperammonemic Encephalopathy

FAVLYXA can cause hyperammonemic encephalopathy in the absence of liver disease or other identifiable cause, based on postmarketing reports. Signs or symptoms of hyperammonemic

encephalopathy began within 72 hours after initiation of FAVLYXA infusion; these included altered mental status, confusion, disorientation, coma, or ataxia, in the presence of concomitant elevated serum ammonia level. Withhold FAVLYXA for hyperammonemic encephalopathy and initiate ammonia-lowering therapy. The risks of resumption of FAVLYXA in patients with hyperammonemic encephalopathy that has resolved have not been established *[see Dosage and Administration (2.3)]*.

5.4 Neurologic Toxicity

FAVLYXA can cause neurologic toxicity, including acute cerebellar syndrome and other neurologic events, based on postmarketing reports. Neurologic symptoms included confusion, disorientation, ataxia, or visual disturbances. Withhold FAVLYXA for neurologic toxicity. There are insufficient data on the risks of resumption of FAVLYXA in patients with neurologic toxicity that has resolved *[see Dosage and Administration (2.3)]*.

5.5 Diarrhea

FAVLYXA can cause severe diarrhea. Withhold FAVLYXA for Grade 3 or 4 diarrhea until resolved or decreased in intensity to Grade 1, then resume FAVLYXA at a reduced dose. Administer fluids, electrolyte replacement, or antidiarrheal treatments as necessary *[see Dosage and Administration (2.3)]*.

5.6 Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome)

FAVLYXA can cause palmar-plantar erythrodysesthesia, also known as hand-foot syndrome (HFS). Symptoms of HFS include a tingling sensation, pain, swelling, and erythema with tenderness, and desquamation. HFS occurs more commonly when fluorouracil is administered as a continuous infusion than when fluorouracil is administered as a bolus injection, and has been reported to occur more frequently in patients with previous exposure to chemotherapy. HFS is generally observed after 8 to 9 weeks of fluorouracil administration but may occur earlier. Institute supportive measures for symptomatic relief of HFS. Withhold FAVLYXA administration for Grade 2 or 3 HFS; resume FAVLYXA at a reduced dose when HFS is completely resolved or decreased in severity to Grade 1 *[see Dosage and Administration (2.3)]*.

5.7 Myelosuppression

FAVLYXA can cause severe and fatal myelosuppression which may include neutropenia, thrombocytopenia, and anemia. The nadir in neutrophil counts commonly occurs between 9 and 14 days after fluorouracil administration. Obtain complete blood counts prior to each treatment cycle, weekly if administered on a weekly or similar schedule, and as needed. Withhold FAVLYXA until Grade 4 myelosuppression resolves; resume FAVLYXA at a reduced dose when myelosuppression has resolved or improved to Grade 1 in severity *[see Dosage and Administration (2.3)]*.

5.8 Mucositis

FAVLYXA can cause mucositis, stomatitis or esophagopharyngitis, which may lead to mucosal sloughing or ulceration.

The incidence is reported to be higher with administration of fluorouracil by intravenous bolus compared with administration by continuous infusion. Withhold FAVLYXA administration for Grade 3 or 4 mucositis; resume FAVLYXA at a reduced dose once mucositis has resolved or decreased in severity to Grade 1 *[see Dosage and Administration (2.3)]*.

5.9 Increased Risk of Bleeding with Concomitant Use of Warfarin

Altered coagulation parameters and/or bleeding, including death, have been reported during concomitant use of warfarin and fluorouracil. Monitor INR more frequently and adjust the dose of warfarin in patients receiving concomitant warfarin *[see Drug Interactions (7)]*.

5.10 Embryofetal Toxicity

Based on its mechanism of action and animal reproduction studies, FAVLYXA can cause fetal harm when administered during pregnancy *[see Use in Specific Populations (8.1), and Clinical Pharmacology (12.1)]*. Advise females of reproductive potential to use effective contraception during treatment with FAVLYXA and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with FAVLYXA and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious adverse reactions or death from Dihydropyrimidine Dehydrogenase (DPD) deficiency *[see Warnings and Precautions (5.1)]*
- Cardiotoxicity *[see Warnings and Precautions (5.2)]*
- Hyperammonemic encephalopathy *[see Warnings and Precautions (5.3)]*
- Neurologic toxicity *[see Warnings and Precautions (5.4)]*
- Diarrhea *[see Warnings and Precautions (5.5)]*
- Palmar-plantar erythrodysesthesia (hand-foot syndrome) *[see Warnings and Precautions (5.6)]*
- Myelosuppression *[see Warnings and Precautions (5.7)]*
- Mucositis *[see Warnings and Precautions (5.8)]*
- Increased risk of bleeding with concomitant use of warfarin *[see Warnings and Precautions (5.9)]*

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fluorouracil. Because these reactions are reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hematologic: pancytopenia *[see Warnings and Precautions (5.7)]*

Gastrointestinal: gastrointestinal ulceration, nausea, vomiting

Allergic Reactions: anaphylaxis and generalized allergic reactions

Neurologic: nystagmus, headache

Dermatologic: dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation

Ophthalmic: lacrimal duct stenosis, visual changes, lacrimation, photophobia

Psychiatric: euphoria

Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails)

7 DRUG INTERACTIONS

7.1 Effect of FAVLYXA on Other Drugs

Vitamin K Antagonists

Monitor INR and PT more frequently in patients receiving FAVLYXA and warfarin. Elevated INR and PT have been reported in patients taking fluorouracil concomitantly with warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on mechanism of action and animal reproduction studies, FAVLYXA can cause fetal harm when administered during pregnancy *[see Clinical Pharmacology (12.1)].* Available data from observational studies with intravenous administration of fluorouracil during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Administration of fluorouracil to rats and mice during selected periods of organogenesis, at doses lower than a human dose of 12 mg/kg, caused embryolethality and teratogenicity. Malformations included cleft palate and skeletal defects. In monkeys, maternal doses of fluorouracil higher than an approximate human dose of 12 mg/kg resulted in abortion *(see Data).*

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

Malformations including cleft palate, skeletal defects and deformed appendages (paws and tails) were observed when fluorouracil was administered by intraperitoneal injection to mice at doses at or above 10 mg/kg (approximately 0.06 times a human dose of 12 mg/kg on a mg/m^2 basis) for 4 days during the period of organogenesis. Similar results were observed in hamsters administered fluorouracil intramuscularly at doses lower than those administered in commonly used clinical treatment regimens. In rats, administration of fluorouracil by intraperitoneal injection at doses greater than 15 mg/kg (approximately 0.2 times a human dose of 12 mg/kg on a mg/m^2 basis) for a single day during organogenesis resulted in delays in growth and malformations including micro-anophthalmos. In monkeys, administration of fluorouracil during organogenesis at doses approximately equal to a human dose of 12 mg/kg on a mg/m^2 basis resulted in abortion; at a 50% lower dose, resorptions and decreased fetal body weights were reported.

8.2 Lactation

Risk Summary

There are no data on the presence of fluorouracil or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients not to breastfeed during treatment with FAVLYXA and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

FAVLYXA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify that females of reproductive potential are not pregnant prior to initiating FAVLYXA *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1, 8.3)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with FAVLYXA and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with FAVLYXA and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility
Based on animal studies, FAVLYXA may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of FAVLYXA in pediatric patients have not been established.

8.5 Geriatric Use

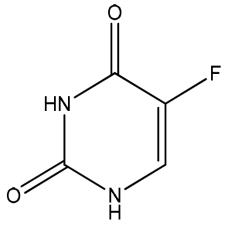
Reported clinical experience has not identified differences in safety or effectiveness between the elderly and younger patients.

10 OVERDOSAGE

Administer uridine triacetate within 96 hours following the end of FAVLYXA infusion for management of fluorouracil overdose.

11 DESCRIPTION

FAVLYXA injection contains fluorouracil, a nucleoside metabolic inhibitor. Fluorouracil, a fluorinated pyrimidine, has a chemical name of 5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione. Its structural formula is:



Molecular formula: $C_4H_3FN_2O_2$
Molecular weight: 130.08 g/mole

FAVLYXA injection 250 mg/10 mL is a sterile, colorless to light yellow clear solution available in single-dose vials for intravenous bolus or infusion administration. Each mL contains 25 mg fluorouracil in water for injection. Sodium hydroxide is added to adjust the pH to 8.6 to 9.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluorouracil is a nucleoside metabolic inhibitor that interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA); these affect rapidly growing cells and may lead to cell death. Fluorouracil is converted to three main active metabolites: 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), 5-fluorouridine-5′triphosphate (FUTP) and 5-fluoro-2′-deoxyuridine-5′-triphosphate (FdUTP).

These metabolites have several effects including the inhibition of thymidylate synthase by FdUMP, incorporation of FUTP into RNA and incorporation of FdUTP into DNA.

12.2 Pharmacodynamics

Fluorouracil exposure-response relationships and the time course of the pharmacodynamic response are unknown.

12.3 Pharmacokinetics

Distribution

Following bolus intravenous injection, fluorouracil distributes throughout the body including the intestinal mucosa, bone marrow, liver, cerebrospinal fluid and brain tissue.

Elimination

Following bolus intravenous injection, 5 to 20% of the parent drug is excreted unchanged in the urine in six hours. The remaining percentage of the administered dose is metabolized, primarily in the liver. The metabolites of fluorouracil (e.g., urea and α-fluoro-ßalanine) are excreted in the urine over 3 to 4 hours.

Following bolus intravenous injection of fluorouracil, as a single agent, the elimination half-life increased with dose from 8 to 20 minutes.

12.5 Pharmacogenomics

The DPYD gene encodes the enzyme DPD, which is responsible for the catabolism of >80% of fluorouracil. Approximately 3 to 5% of White populations have partial DPD deficiency and 0.2% of White populations have complete DPD deficiency, which may be due to certain genetic no function or decreased function variants in DPYD resulting in partial to complete or near complete absence of enzyme activity. DPD deficiency is estimated to be more prevalent in Black or African American populations compared to White populations. Insufficient information is available to estimate the prevalence of DPD deficiency in other populations.

Patients who are homozygous or compound heterozygous for no function DPYD variants (i.e., carry two *DPYD* variants that result in no DPD enzyme activity) or are compound heterozygous for a no function DPYD variant plus a decreased function DPYD variant have complete DPD deficiency and are at increased risk for acute early-onset of toxicity and serious life-threatening, or fatal adverse reactions due to increased systemic exposure to fluorouracil. Partial DPD deficiency can result from the presence of either two decreased function *DPYD* variants or one normal function plus either a decreased function or a no function *DPYD* variant. Patients with partial DPD deficiency may also be at an increased risk for toxicity from fluorouracil.

Several *DPYD* variants observed with variability across populations have been associated with reduced or no DPD activity, especially when present as homozygous or compound heterozygous variants. These include c.1905+1G>A (*DPYD* *2A), c.1679T>G (*DPYD* *13), c.2846A>T, and

c.1129-5923C>G (Haplotype B3). *DPYD**2A and *DPYD**13 are no function variants, and c.2846A>T, c.1129-5923C>G, and c557A>G are decreased function variants. This is not a complete listing of all *DPYD* variants that may result in DPD deficiency *[see Warnings and Precautions (5.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with fluorouracil. Fluorouracil was mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and induced chromosomal aberrations in hamster fibroblasts *in vitro* and in mouse bone marrow in the *in vivo* mouse micronucleus assay.

Administration of fluorouracil intraperitoneally to male rats at dose levels equal to or greater than 1.7-fold the human dose of 12 mg/kg induced chromosomal aberrations in spermatogonia and inhibition of spermatogonia differentiation resulting in transient infertility. In female rats, intraperitoneal administration of fluorouracil during the pre-ovulatory phases of oogenesis at dose levels equal to or greater than 0.33 times a human dose of 12 mg/kg resulted in decreased incidence of fertile matings, increased pre-implantation loss, and fetotoxicity.

15 REFERENCES

"OSHA Hazardous Drugs." *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FAVLYXA™ Injection is a sterile colorless to light yellow clear solution available in single-dose vials individually packaged in a carton as follows:

NDC Number	Strength	Package
83831-143-01	250 mg/10 mL (25 mg/mL)	1 single-dose vial in 1 carton

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]. Protect from light. Retain in carton until time of use.

Fluorouracil is a hazardous drug. Follow applicable special handling and disposable procedures *[see References (15)]*.

17 PATIENT COUNSELING INFORMATION

Advise patients of the following:

Serious Adverse Reactions or Death from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Prior to initiating FAVLYXA treatment, inform patients of the potential for serious or fatal adverse reactions due to DPD deficiency and testing for genetic variants of *DPYD*. Advise patients to immediately contact their healthcare provider if symptoms of severe mucositis, diarrhea, neutropenia, and neurotoxicity occur *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]*.

Cardiotoxicity

Advise patients of the risk of cardiotoxicity and to immediately contact their healthcare provider for new onset of chest pain, shortness of breath, dizziness, or lightheadedness *[see Warnings and Precautions (5.2)]*.

Hyperammonemic Encephalopathy and Neurologic Toxicity

Advise patients to immediately contact their healthcare provider or go to an emergency room for new onset of confusion, disorientation, or otherwise altered mental status; difficulty with balance or coordination; or visual disturbances *[see Warnings and Precautions (5.3, 5.4)]*.

Diarrhea

Inform patients experiencing grade 2 or higher diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or experiencing severe bloody diarrhea with severe abdominal pain and fever to immediately contact their health care provider. Advise patients on the use of antidiarrheal treatments (e.g., loperamide) to manage diarrhea *[see Warnings and Precautions (5.5)]*.

Palmar-Plantar Erythrodysesthesia Syndrome

Instruct patients experiencing grade 2 palmar-plantar erythrodysesthesia syndrome or greater to stop taking FAVLYXA immediately and to contact their healthcare provider. Inform patients that initiation of symptomatic treatment is recommended, and hand-and-foot syndrome can lead to loss of fingerprints which could impact personal identification *[see Warnings and Precautions (5.6)]*.

Myelosuppression

Inform patients who develop a fever of 100.5°F or greater or other evidence of potential infection to immediately contact their healthcare provider *[see Warnings and Precautions (5.7)]*.

Mucositis

Inform patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater to contact their healthcare provider *[see Adverse Reactions (5.8)]*.

Increased Risk of Bleeding with Concomitant Warfarin

Advise patients taking warfarin, that they are at an increased risk of severe bleeding while taking FAVLYXA. Advise these patients that INR should be monitored more frequently, and dosage modifications of warfarin may be required, while taking and after discontinuation of FAVLYXA. Advise these patients to immediately contact their healthcare provider if signs or symptoms of bleeding occur *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with FAVLYXA and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.
Advise males with female partners of reproductive potential to use effective contraception during treatment with FAVLYXA and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation
Advise females not to breastfeed during treatment with FAVLYXA and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility
Advise males and females of reproductive potential that FAVLYXA may impair fertility *[see Use in Specific Populations (8.3)]*.

Drug interactions
Advise patients to notify their healthcare provider of all drugs they are taking, including warfarin or other coumarin-derivative anticoagulants. Advise patients of the importance of keeping appointments for blood tests *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

Rx Only

Manufactured for:
Avyxa Pharma, LLC
New Jersey 07054, USA

Made in China

AVYXA

Revised: 02/2026

ARTWORK INFORMATION		
Product Name:	FAVLYXA™ (fluorouracil) Injection, USP	**Printable Colors : 5** 300 C, 7488 C, BLACK C, 256 C, 2035 C
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Font Type:	Helvetica condensed	
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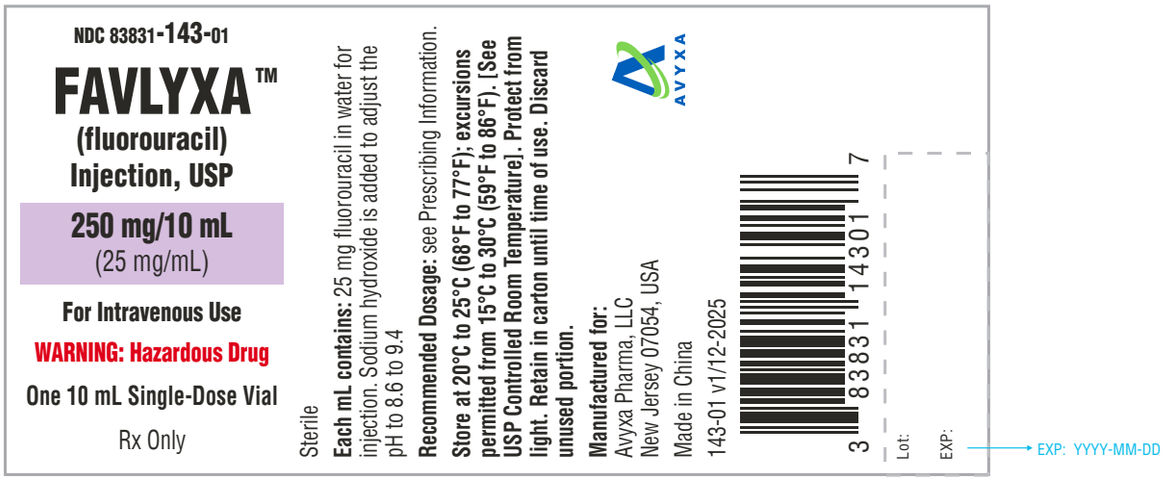
Reference ID: 5748827



ARTWORK INFORMATION		
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Dimension:	67.2 x 32mm	
Font size:	7.0 pt	
Font Type:	Helvetica condensed	
Creation Date:	10-27-2025	

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/s/

STEVEN J LEMERY
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