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FEBUXOSTAT

FEBUXORIN
40mg Film-coated Tablet
Anti-gout
(Preparation Inhibiting Uric Acid Production)

℞

COMPOSITION
Each film-coated tablet contains:
Febuxostat …… 40 mg

PRODUCT DESCRIPTION
Green colored, round, biconvex, film coated tablets.

PHARMACODYNAMICS
Pharmacotherapeutic group: Belongs to the class of preparations inhibiting uric acid production. Used in the treatment of gout. ATC code: M04AA03
Mechanism of action
Febuxostat is a xanthine oxidase inhibitor. The active ingredient in Febuxostat T is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.
Febuxostat, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.
Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, Febuxostat resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg daily dose.
Effect on Cardiac Rapolarization: The effect of Febuxostat on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. Febuxostat in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

PHARMACOKINETICS
In healthy subjects, maximum plasma concentrations (C_{max}) and AUC of Febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t1/2) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy subjects.
Absorption
The absorption of radiolabeled Febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of Febuxostat occurred between 1 and 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg/ml (N=30), and 2.6 ± 1.7 mcg/ml (N=227), respectively. Absolute bioavailability of the Febuxostat tablet has not been studied. Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, Febuxostat may be taken without regard to food. Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80mg single dose of Febuxostat has been shown to delay absorption of febuxostat (approximately one hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC_{24}. As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, Febuxostat may be taken without regard to antacid use.
Distribution
The mean apparent steady state volume of distribution (Vss/F) of Febuxostat was approximately 50 L (CV~40%). The plasma protein binding of Febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg doses.
Metabolism: Febuxostat is extensively metabolized by both conjugation via uridine diphosphateglucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of Febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than Febuxostat. In urine and feces, acyl glucuronide metabolites of Febuxostat (35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of Febuxostat in vivo.
Elimination
Febuxostat is eliminated by both hepatic and renal pathways. The apparent mean terminal elimination half-life (t1/2) of Febuxostat was approximately 5 to 8 hours. Following an 80mg oral dose of 14C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).
Special populations
Pediatric Use
The pharmacokinetics of Febuxostat in patients under the age of 18 years have not been studied.
Geriatric Use
The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of Febuxostat in geriatric subjects (≥65 years) were similar to those in younger subjects (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger subjects. No dose adjustment is necessary in geriatric patients.
Renal Impairment
Following multiple 80 mg doses of Febuxostat in healthy subjects with mild (Clcr 50 to 80mL/min), moderate (Clcr 30 to 49 mL/min) or severe renal impairment (Clcr 10 to 29 mL/min), the C_{max} of febuxostat did not change relative to subjects with normal renal function (Clcr greater than 80 mL/min). AUC and half-life of febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in subjects with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for three active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for subjects with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).
No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended starting dose of Febuxostat is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/mL after two weeks with 40 mg, Febuxostat 80 mg is recommended. There is insufficient data in patients with severe renal impairment; caution should be exercised in those patients.
Febuxostat has not been studied in end stage renal impairment patients who are on dialysis.
Hepatic Impairment
Following multiple 80 mg doses of Febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to subjects with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients.
Gender
Following multiple oral doses of Febuxostat, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.
Race
No specific pharmacokinetic study was conducted to investigate the effects of race.
Drug-Drug Interactions
Effect of Febuxostat on Other Drugs: Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of Febuxostat upon the pharmacokinetics of theophylline (an XO substrate) in healthy subjects showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline.
Drug interaction studies of Febuxostat with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by Febuxostat may cause increased plasma concentrations of these drugs leading to toxicity. Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.
Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although Febuxostat drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because Febuxostat is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.
P450 Substrate Drugs: *In vitro* studies have shown that Febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3M at clinically relevant concentrations. As such, pharmacokinetic interactions between Febuxostat and drugs metabolized by these CYP enzymes are unlikely.
Effect of Other Drugs on Febuxostat: Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between Febuxostat and a drug that inhibits or induces one particular enzyme isoform is in general not expected.
In Vivo Drug Interaction Studies*:*
Theophylline: No dose adjustment is necessary for theophylline when coadministered with Febuxostat. Administration of Febuxostat (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by Febuxostat. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to coadminister Febuxostat and theophylline.
Colchicine: No dose adjustment is necessary for either Febuxostat or colchicine when the two drugs are coadministered. Administration of Febuxostat (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with Febuxostat (120 mg daily) resulted in a less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.
Naproxen: No dose adjustment is necessary for Febuxostat or naproxen when the two drugs are coadministered. Administration of Febuxostat (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).
Indomethacin: No dose adjustment is necessary for either Febuxostat or indomethacin when these two drugs are coadministered. Administration of Febuxostat (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).
Hydrochlorothiazide: No dose adjustment is necessary for Febuxostat when coadministered with hydrochlorothiazide. Administration of Febuxostat (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.
Warfarin: No dose adjustment is necessary for warfarin when coadministered with Febuxostat. Administration of Febuxostat (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the coadministration of Febuxostat.
Desipramine: Coadministration of drugs that are CYP2D6 substrates (such as desipramine) with Febuxostat are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of Febuxostat (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

INDICATIONS
Febuxostat is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
It is also indicated for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

DOSAGE AND MODE OF ADMINISTRATION
Dosage
For treatment of hyperuricemia in patients with gout, Febuxostat is recommended at 20mg or 40mg once daily. Or as prescribed by the physician.
Method of administration
The recommended starting dose of Febuxostat is 20mg or 40mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks with 20mg or 40mg, higher doses are recommended. Febuxostat can be taken without regard to food or antacid use.
Use in special population
Safety and effectiveness in pediatric patients under 18 years of age have not been established. No dose adjustment is necessary when administering Febuxostat in patients with mild to moderate renal impairment. There are insufficient data in patients with severe renal impairment (Clcr less than 30 mL/min); therefore, caution should be exercised in these patients. No dose adjustment is necessary in patients with mild to

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moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients.
Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating Febuxostat therapy.
Gout flares may occur after initiation of Febuxostat due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. If a gout flare occurs during Febuxostat treatment, Febuxostat need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of Febuxostat. Prophylactic therapy may be beneficial for up to six months.
Use in Geriatric population
No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of Febuxostat, 16% were 65 and over, while 4% were 75 and over. Comparing subjects in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of Febuxostat in geriatric subjects ≥65 years) were similar to those in younger subjects (18 to 40 years).
Use in patients with Secondary hyperuricemia
No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients): Febuxostat is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

CONTRAINDICATION(S)
Febuxostat is contraindicated in patients: being treated with azathioprine or mercaptopurine, or with a history of hypersensitivity to Febuxostat or to any other ingredient in the formulation. Pregnancy and breastfeeding.

WARNING(S) AND PRECAUTION(S)
Gout Flare
After initiation of Febuxostat, an increase in gout flares is frequently observed. In order to prevent gout flares when Febuxostat is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended.
Cardiovascular Events
In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with Febuxostat.
Monitor for signs and symptoms of myocardial infarction (MI) and stroke.
Hepatic Effects
There have been post-marketing reports of fatal and non-fatal hepatic failure in patients taking Febuxostat, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST 2%, 2%, and ALT: 3%, 2% in Febuxostat and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted. Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating Febuxostat. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), Febuxostat treatment should be interrupted and investigation done to establish the probable cause. Febuxostat should not be restarted in these patients without another explanation for the liver test abnormalities. Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug induced liver injury and should not be restarted on Febuxostat. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with Febuxostat can be used with caution.
Effects on Ability to Drive and Use Machine
No studies on the effects on the ability to drive or use machines have been performed. Caution should be exercised before driving or using machinery.

INTERACTIONS
Xanthine Oxidase Substrate Drugs
Febuxostat is an XO inhibitor. Based on a drug interaction study in healthy subjects, Febuxostat altered the metabolism of theophylline (a substrate of XO) in humans. Therefore, use with caution when coadministering Febuxostat with theophylline. Drug interaction studies of Febuxostat with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by Febuxostat may cause increased plasma concentrations of these drugs leading to toxicity. Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.
Drug interaction studies of Febuxostat with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of Febuxostat during cytotoxic chemotherapy. Based on drug interaction studies in healthy subjects, Febuxostat does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine. Therefore, Febuxostat may be used concomitantly with these medications.

PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category C:
There are no adequate and well-controlled studies in pregnant women. Febuxostat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Febuxostat was not teratogenic in rats and rabbits at oral doses up to 48 mg/kg (40 and 51 times the human plasma exposure at 80 mg/day for equal body surface area, respectively) during organogenesis. However, increased neonatal mortality and a reduction in the neonatal body weight gain were observed when pregnant rats were treated with oral doses up to 48 mg/kg (40 times the human plasma exposure at 80 mg/day) during organogenesis and through lactation period.
Nursing Mothers:
Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Febuxostat is administered to a nursing woman.

ADVERSE DRUG REACTION
The most common adverse drug reaction seen in patients taking Febuxostat tablet are liver function abnormalities, nausea, arthralgia and rash.
Less Common Adverse Reactions
Blood and Lymphatic System Disorders
Anemia, idiopathic thrombocytopenic purpura, Leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.
Cardiac Disorders
Angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.
Ear and Labyrinth Disorders
Deafness, tinnitus, vertigo.
Eye Disorders
Vision blurred.
Gastrointestinal Disorders
Abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, hematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.
General Disorders and Administration Site Conditions
Asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.
Hepatobiliary Disorders
Cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.
Immune System Disorder
Hypersensitivity.
Infections and Infestations
Herpes zoster.
Procedural Complications
Contusion.
Metabolism and Nutrition Disorders
Anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.
Musculoskeletal and Connective Tissue Disorders
Arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.
Nervous System Disorders
Altered taste, balance disorder, cerebrovascular accident, Guillain-Barre syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, and tremor.
Psychiatric Disorders
Agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.
Renal and Urinary Disorders
Hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.
Reproductive System and Breast Changes
Breast pain, erectile dysfunction, gynecomastia.
Respiratory, Thoracic and Mediastinal Disorders
Bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.
Skin and Subcutaneous Tissue Disorders
Alopecia, angioedema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/altered pigmentation, skin lesion, skin odor abnormal, urticaria.
Vascular Disorders
Flushing, hot flush, hypertension, hypotension.
Hepatobiliary Disorders
Hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.
Immune System Disorders
Anaphylaxis, anaphylactic reaction.
Musculoskeletal and Connective Tissue Disorders
Rhabdomyolysis.
Psychiatric Disorders
Psychotic behavior including aggressive thoughts.
Renal and Urinary Disorders
Tubulointerstitial nephritis.
Skin and Subcutaneous Tissue Disorders
Generalized rash, Stevens Johnson Syndrome, hypersensitivity skin reactions.

OVERDOSE
No overdose of Febuxostat was reported. Patients should be managed by symptomatic and supportive care should there be an overdose.

STORAGE CONDITION: Store at temperatures not exceeding 30°C. Protect from light.
Keep out of the reach of children.

SHELF LIFE: 36 months

DOSAGE FORM AND PACK SIZE:
Alu/Alu blister pack x 10 (Box of 10's and 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL
No special requirements.

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA:
www.fda.gov.ph
Patient should seek medical attention immediately at the first sign of any adverse drug reaction.

DATE OF FIRST AUTHORISATION: August 2023

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