Azathioprine (Imuran®)

Azathioprine is an imidazolyl derivative of 6-mercaptopurine and its metabolites are incorporated into DNA to halt replication as well as block the pathway for purine synthesis. The immunosuppressive antimetabolites, including 6-thioguanine nucleotide, suppress disease manifestations and underlying pathology of autoimmune inflammatory disease. Azathioprine is considered a slow-acting drug and effects may persist after the drug has been discontinued.

Resources from Manufacturer

Full Prescribing Information

Indications and Dosing in Rheumatology

FDA-approved indications

Adults:

- **Rheumatoid Arthritis (RA)***
  - Initial dosage: 1 mg/kg/day (50 to 100 mg) given as a single dose or twice-daily schedule
  - Dose may be increased after 6-8 weeks by 0.5 mg/kg increments at 4-week intervals if there are no serious toxicities and initial response is unsatisfactory to a maximum dose of 2.5 mg/kg per day
  - Therapeutic response occurs after several weeks (~6-8) and an adequate trial should be a minimum of 12 weeks
  - Maintenance therapy: use the lowest effective dose with dose adjustments in 0.5 mg/kg (or approximately 25 mg/day) increments every 4 weeks
  - Azathioprine can be discontinued abruptly, but delayed effects are possible

Other off-label uses:

- **Behçet syndrome:** 50 mg once daily, may increase by 50 mg every 4 weeks as tolerated to goal maintenance dose of 2.5 mg/kg once daily
- **Lupus nephritis:** 50 mg once daily, may increase by 50 mg increments (or 0.5 mg/kg/day) every 4 weeks as tolerated to a goal maintenance dose of ~2 mg/kg once daily
- **Sarcoidosis:** 25 mg to 50 mg once daily, may increase by 50 mg every 2-4 weeks as tolerated to a goal maintenance dose of ~2 mg/kg once daily
- **Uveitis:** 2-3 mg/kg once daily not to exceed 250 mg/day
- **Pediatrics**
  - **Lupus nephritis:** 2–2.5 mg/kg once daily
  - **Uveitis:** mean 2.4 mg/kg once daily with reported range 1.4–3.2 mg/kg daily

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Contraindications

- Known hypersensitivity to azathioprine
- Use in pregnant women
- Patients previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan, or others) may have a prohibitive risk of malignancy if treated with azathioprine

Warnings and Precautions

- **Malignancy:** Patient receiving immunosuppression including azathioprine are at increased risk of developing lymphoma and other malignancies, particularly of the skin. The risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients.
- **Cytopenia:** Severe leukopenia, thrombocytopenia, anemias, and/or pancytopenia may occur in patients being treated with azathioprine. Hematologic toxicities are dose-related.
- **Serious infections:** Patients receiving immunosuppressants, including azathioprine, are at increased risk for bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections. These infections may lead to serious, including fatal outcomes.
- **Effect on sperm and pregnancy:** Azathioprine has been reported to cause temporary depression in spermatogenesis and reduction in sperm viability and count in animal studies. Azathioprine may cause fetal harm when administered to a pregnant woman and should be avoided whenever possible.
- **TPMT and NUDT15 testing:** Consider genotyping or phenotyping patients for TPMT deficiency and genotyping for NUDT15 deficiency in patients with severe myelosuppression.
- **Drug interactions with xanthine oxidase (XO) inhibitors:** One of the pathways for azathioprine inactivation is inhibited by XO inhibitors (allopurinol or febuxostat), leading to increased plasma concentration of azathioprine or its metabolite 6-MP. Patients receiving azathioprine and allopurinol concomitantly should have a dose reduction of azathioprine to ⅓–¼ the usual dose. Concomitant use of azathioprine and febuxostat is not recommended.
- **Drug interactions with Neuromuscular agents:** For patient undergoing surgery, azathioprine can potentiate the neuromuscular block (ex: succinylcholine). In most cases should be held prior to surgery and inform anesthesiologist of azathioprine use.
- **Vaccines:** May have diminished response to vaccines.

Common Adverse Reactions

Common side effects include: nausea and vomiting, leukopenia and infections

Medication Strength and Storage

- Available as 50 mg, 75 mg, and 100 mg oral tablets
- Store tablets at room temperature (68°F to 77°F) in a dry place and protect from light

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Medication Administration and Storage

- Administration after meals or in divided doses may decrease adverse GI events
- Patients on azathioprine should have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly thereafter or more frequently if dosage alterations or other therapy changes are necessary.

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