Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

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# Azathioprine Tablets I.P. 50mg

## ARETHA® अरिथा

**Composition:**
Each film coated tablet contains:
Azathioprine I.P. 50 mg
Excipients q.s.
**Colour:** Titanium Dioxide I.P.

**PHARMACEUTICAL FORM**
Tablets

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

**Pharmacotherapeutic group**: Other immunosuppressants
ATC code: L04AX01

**Mechanism of Action**
Azathioprine is an immunosuppressive antimetabolite; an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down *in vivo* into 6-MP and a methyl-nitroimidazole moiety. 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid.

The precise mode of action of azathioprine remains to be elucidated. By antagonizing purine metabolism, it may inhibit RNA and DNA synthesis, and hence prevent the proliferation of cells involved in the immune response. Suggested mechanisms include:

- The activity of 6-MP as a purine antimetabolite.
- The possible blockade of -SH groups by alkylation.
- Damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.

Given these nature of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment.

**Pharmacokinetic Properties**
***Absorption***
Azathioprine is well absorbed following oral administration. Maximum serum radioactivity occurs at 1 to 2 hours after oral $^{35}$S-azathioprine and decays with a half-life of 5 hours. This is not an estimate of the half-life of azathioprine itself, but is the decay rate for all $^{35}$S-containing metabolites of the drug. Because of extensive metabolism, only a fraction of the radioactivity is present as azathioprine. Usual doses produce low blood levels (<1 mcg/mL) of azathioprine and mercaptopurine derived from it. Blood levels are of little predictive value for therapy since the magnitude and duration of clinical effects correlate with thiopurine nucleotide levels in tissues, rather than levels in plasma.

***Distribution***
Azathioprine and mercaptopurine are moderately bound to serum proteins (30%) and are partially dialyzable (see **Overdose section).**

***Metabolism***
Azathioprine is metabolized to 6-MP. Activation of 6-MP occurs via hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and a series of multi-enzymatic processes involving kinases to form 6-thioguanine nucleotides (6-TGNs) as major metabolites (see **Metabolism Scheme in Figure 1**). The cytotoxicity of azathioprine is due, in part, to the incorporation of 6-TGN into DNA.


**Figure 1: Metabolism Pathway of Azathioprine: Competing pathways result in inactivation by TPMT or XO, or incorporation of cytotoxic nucleotides into DNA.**

(GMPS: guanosine monophosphate synthetase; HGPRT: hypoxanthine-guanine phosphoribosyl-transferase; IMPD: inosine monophosphate dehydrogenase; MeMP: methylmercaptopurine; MeMPN: methylmercaptopurine nucleotide; TGN: thioguanine nucleotides; TIMP: thioinosine monophosphate; TPMT: thiopurine S-methyltransferase; TU: thiouric acid; XO: xanthine oxidase; MP: mercaptopurine).

6-MP undergoes two major inactivation routes (Figure 1). One is thiol methylation, which is catalyzed by the enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite 6-methylmercaptopurine (6-MeMP). TPMT activity is controlled by a genetic polymorphism. Approximately 10% of Caucasians and African Americans, inherit one non-functional TPMT allele (heterozygous) conferring intermediate TPMT activity; and 0.3% inherit two TPMT non-functional alleles (homozygous) conferring low or absent TPMT activity. Non-functional alleles are less common in Asians. Patients with intermediate TPMT activity may be at increased risk of myelotoxicity if receiving conventional doses of azathioprine tablets. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of azathioprine tablets. TPMT genotyping or phenotyping (red blood cell TPMT activity) can help identify patients who are at an increased risk for developing toxicity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions (see **Special Warnings and Precautions for Use** and **Undesirable Effects** section).

Another inactivation pathway is oxidation; 6-MP is catalyzed by XO to form 6-thiouric acid (6-TU). The inhibition of XO in patients receiving allopurinol is the basis for the azathioprine dosage reduction required in these patients (see **Posology and Method of Administration** section).

The proportions of azathioprine metabolites are different in individual patients, which presumably accounts for the variable magnitude and duration of drug effects.

***Excretion***
Azathioprine and 6-MP are rapidly eliminated from blood and are oxidized or methylated in erythrocytes and liver; no azathioprine or mercaptopurine is detectable in urine after 8 hours. Renal clearance is probably not important in predicting biological effectiveness or toxicities, although dose reduction is practiced in patients with poor renal function.

**Precilnical Safety Data**
Teratogenicity or embryolethality has been seen in a number of animal species, with a varying degree of susceptibility.

In rabbits, a dose of 5-15 mg/kg body weight daily on days 6-14 of pregnancy produced skeletal abnormalities; in mice and rats, doses of 1-2 mg/kg body weight daily on days 3-12 were lethal to the embryos.

Azathioprine was mutagenic in a number of *in-vitro* and *in-vivo* genotoxicity assays.

In long-term carcinogenicity studies of azathioprine in mice and rats, an increased incidence of lymphosarcomas (mice) and epithelial tumours and carcinomas (rats) were observed at dosages that were up to 2-fold the human therapeutic dosage.

**CLINICAL PARTICULARS**
**Therapeutic Indications**
Azathioprine is indicated as an adjunct for the prevention of rejection in renal homotransplantation.It is also indicated for the management of active rheumatoid arthritis to reduce signs and symptoms.

Aspirin, non-steroidal anti-inflammatory drugs and/or low dose glucocorticoids may be continued during treatment with azathioprine.

**Posology and Method of Administration**
**TPMT testing cannot substitute for complete blood count (CBC) monitoring in patients receiving azathioprine tablets.** TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity (homozygous for non-functional alleles) are at an increased risk of developing severe, life-threatening myelotoxicity from azathioprine tablets, if conventional doses are given. Physicians may consider alternative therapies for such patients.

Azathioprine tablets should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity; toxicity may result if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction.

***Renal Homotransplantation***
The dose of azathioprine tablets required to prevent rejection and minimize toxicity will vary with individual patients, which necessitates careful management. The initial dose is usually 3 to 5 mg/kg daily, beginning at the time of transplant. Azathioprine tablets are usually given as a single daily dose starting on the day of, and in a minority of cases 1 to 3 days before, transplantation. Dose reduction to maintenance levels of 1 to 3 mg/kg daily is usually possible. The dose of azathioprine tablets should not be increased to toxic levels if graft rejection is suspected. Discontinuation may be necessary to avoid severe hematologic or other toxicity, even if rejection of the homograft may be a consequence of drug withdrawal.

***Rheumatoid Arthritis***
Azathioprine tablets are usually given on a daily basis. The initial dose should be approximately 1.0 mg/kg (50 to 100 mg) given as a single dose or on a twice-daily schedule. The dose may be increased, beginning at 6 to 8 weeks and thereafter by steps at 4-week intervals, if there are no serious toxicities and if initial response is unsatisfactory. Dose increments should be 0.5 mg/kg daily, up to a maximum dose of 2.5 mg/kg per day. Therapeutic response occurs after several weeks of treatment, usually 6 to 8; an adequate trial should be a minimum of 12 weeks. Patients not improved after 12 weeks can be considered refractory. Azathioprine tablets may be continued long-term in patients with clinical response, but patients should be monitored carefully, and gradual dosage reduction should be attempted to reduce risk of toxicities.

Maintenance therapy should be at the lowest effective dose. The dose can be lowered decrementally by every 4 weeks 0.5 mg/kg (approximately 25 mg) per day, while other therapy is kept constant. The optimum duration of maintenance of azathioprine tablets has not been determined. Azathioprine tablets can be discontinued abruptly, but delayed effects are possible.

***Use in Renal Dysfunction***
Relatively oliguric patients, especially those with tubular necrosis in the immediate post-cadaveric transplant period, may have delayed clearance of azathioprine tablets or its metabolites, may be particularly sensitive to this drug, and are usually given lower doses. Procedures for proper handling and disposal of this immunosuppressive antimetabolite drug should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**Contraindications**
Azathioprine tablets should not be given to:
- Patients with hypersensitivity to the drug
- Pregnant women with rheumatoid arthritis
- Patients previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan, or others). These patients may run a prohibitive risk of malignancy if treated with azathioprine tablets.

**Special Warnings and Precautions for Use**
Chronic immunosuppression with azathioprine increases *risk of malignancy* in humans. Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women, and with possible hematologic toxicities. Physicians should inform patients of the risk of malignancy with azathioprine. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

***General***
A gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting has been reported. These symptoms may also be accompanied by diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, and occasionally, hypotension. Symptoms of gastrointestinal toxicity most often develop within the first several weeks of therapy with azathioprine tablets and are reversible upon discontinuation of the drug. The reaction can recur within hours after rechallenge with a single dose of azathioprine tablets.

***Post-transplant***
Renal transplant patients are known to have an increased risk of malignancy; predominantly skin cancer and reticulum cell or lymphomatous tumors. The risk of post-transplant lymphomas may be increased in patients who receive aggressive treatment with immunosuppressive drugs, including azathioprine. Therefore, immunosuppressive drug therapy should be maintained at the lowest effective levels.

***Rheumatoid Arthritis***
Information is available on the risk of malignancy with the use of azathioprine in rheumatoid arthritis (see **Undesirable Effects** section**).** It has not been possible to define the precise risk of malignancy due to azathioprine. The data suggest the risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients. However, acute myelogenous leukemia as well as solid tumors has been reported in patients with rheumatoid arthritis who have received azathioprine.



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***Inflammatory Bowel Disease***
Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with azathioprine. These cases have had a very aggressive disease course and have been fatal. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis, and the majority was in adolescent and young adult males. Some of the patients were treated with azathioprine as monotherapy and some had received concomitant treatment with a TNFα blocker at or prior to diagnosis. The safety and efficacy of azathioprine for the treatment of Crohn's disease and ulcerative colitis have not been established.

***Cytopenias***
Severe leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia may occur in patients being treated with azathioprine. Severe bone marrow suppression may also occur. Patients with intermediate TPMT activity may be at an increased risk of myelotoxicity if receiving conventional doses of azathioprine. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of azathioprine. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing azathioprine toxicity.

Hematologic toxicities are dose-related and may be more severe in renal transplant patients whose homograft is undergoing rejection. It is suggested that patients on azathioprine have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary. Delayed hematologic suppression may occur. Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in or persistently low leukocyte count, or other evidence of bone marrow depression. Leukopenia does not correlate with therapeutic effect; therefore the dose should not be increased intentionally to lower the white blood cell count.

***Serious Infections***
Serious infections are a constant hazard for patients receiving chronic immunosuppression, especially for homograft recipients. Fungal, viral, bacterial, and protozoal infections may be fatal and should be treated vigorously. Reduction of azathioprine dosage and/or use of other drugs should be considered.

***Effect on Sperm in Animals***
Azathioprine has been reported to cause temporary depression in spermatogenesis, reduction in sperm viability and reduction in sperm count in mice at doses 10 times the human therapeutic dose. A reduced percentage of fertile matings occurred when animals received 5 mg/kg.

**Drug Interactions**
***Use with Allopurinol***
One of the pathways for inactivation of azathioprine is inhibited by allopurinol. Patients receiving azathioprine tablets and allopurinol concomitantly should have a dose reduction of azathioprine tablets, to approximately one-third to one-fourth the usual dose. It is recommended that a further dose reduction or alternative therapies be considered for patients with low or absent TPMT activity receiving azathioprine tablets and allopurinol because both TPMT and XO inactivation pathways are affected (see **Special Warnings and Precautions for Use** and **Undesirable Effects** sections).

***Use with Aminosalicylates***
There is *in vitro* evidence that aminosalicylate derivatives (e.g., sulphasalazine, mesalazine, or olsalazine) inhibit TPMT. Caution should be used when giving these agents concomitantly with azathioprine tablets.

***Use with Other Agents Affecting Myelopoesis***
Drugs which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.

***Use with Angiotensin-Converting Enzyme Inhibitors***
The use of angiotensin-converting enzyme inhibitors to control hypertension in patients on azathioprine has been reported to induce anemia and severe leukopenia.

***Use with Warfarin***
Azathioprine tablets may inhibit the anticoagulant effect of warfarin.

***Use with Ribavirin***
The use of ribavirin for hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioionosine monophosphate (6MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary.

**Pregnancy and Lactation**
***Pregnancy Category D***
Azathioprine tablets can cause fetal harm when administered to a pregnant woman. Azathioprine tablets should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, use of azathioprine tablets in pregnant patients should be avoided. This drug should not be used for treating rheumatoid arthritis in pregnant women.

Azathioprine tablets are teratogenic in rabbits and mice when given in doses equivalent to the human dose (5 mg/kg daily). Abnormalities included skeletal malformations and visceral anomalies.

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on azathioprine tablets. In a detailed case report, documented lymphopenia, diminished IgG and IgM levels, cytomegalovirus (CMV) infection, and a decreased thymic shadow were noted in an infant born to a mother receiving 150 mg azathioprine and 30 mg prednisone daily throughout pregnancy. At 10 weeks most features were normalized. "DeWitte et al" reported pancytopenia and severe immune deficiency in a preterm infant whose mother received 125 mg azathioprine and 12.5 mg prednisone daily. There have been two published reports of abnormal physical findings. "Williamson and Karp" described an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. "Tallent et al" described an infant with a large myelomeningocele in the upper lumbar region, bilateral dislocated hips, and bilateral talipes equinovarus. The father was on long-term azathioprine therapy.

Benefit versus risk must be weighed carefully before use of azathioprine tablets in patients of reproductive potential. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

***Lactation***
The use of azathioprine tablets in nursing mothers is not recommended. Azathioprine or its metabolites are transferred at low levels, both transplacentally and in breast milk. Because of the potential for tumorigenicity shown for azathioprine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Effects on Ability to Drive And Use Machines**
Not known

**Undesirable Effects**
The principal and potentially serious toxic effects of azathioprine tablets are hematologic and gastrointestinal. The risks of secondary infection and malignancy are also significant (see **Special Warnings and Precautions for Use** section**).** The frequency and severity of adverse reactions depend on the dose and duration of azathioprine tablets as well as on the patient's underlying disease or concomitant therapies. The incidence of hematologic toxicities and neoplasia encountered in groups of renal homograft recipients is significantly higher than that in studies employing azathioprine tablets for rheumatoid arthritis. The relative incidences in clinical studies are summarized below:

| Toxicity | Renal Homograft | Rheumatoid Arthritis |
|---|---|---|
| **Leukopenia (any degree)** | >50% | 28% |
| **<2,500 cells/mm$^3$** | 16% | 5.3% |
| **Infections** | 20% | <1% |
| **Neoplasia** | - | * |
| **Lymphoma** | 0.5% | - |
| **Others** | 2.8% | - |

*Data on the rate and risk of neoplasia among persons with rheumatoid arthritis (RA) treated with azathioprine are limited. The incidence of lymphoproliferative disease in patients with RA appears to be significantly higher than that in the general population. In one completed study, the rate of lymphoproliferative disease in RA patients receiving higher than recommended doses of azathioprine (5 mg/kg per day) was 1.8 cases per 1000 patient-years of follow-up, compared with 0.8 cases per 1000 patient-years of follow-up in those not receiving azathioprine. However, the proportion of the increased risk attributable to the azathioprine dosage or to other therapies (i.e., alkylating agents) received by patients treated with azathioprine cannot be determined.

***Hematologic***
Leukopenia and/or thrombocytopenia are dose-dependent and may occur late in the course of therapy with azathioprine tablets. Dose reduction or temporary withdrawal may result in reversal of these toxicities. Infection may occur as a secondary manifestation of bone marrow suppression or leukopenia; but the incidence of infection in renal homotransplantation is 30 to 60 times that in rheumatoid arthritis. Anemias, including macrocytic anemia and/or bleeding have been reported.

TPMT genotyping or phenotyping can help identify patients with low or absent TPMT activity (homozygous for non-functional alleles), who are at increased risk for severe, life-threatening myelosuppression from azathioprine tablets (see **Special Warnings and Precautions for Use** section**).** Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine.

***Gastrointestinal***
Nausea and vomiting may occur within the first few months of therapy with azathioprine tablets, and occurred in approximately 12% of 676 rheumatoid arthritis patients. The frequency of gastric disturbance often can be reduced by administration of the drug in divided doses and/or after meals. However, in some patients, nausea and vomiting may be severe and may be accompanied by symptoms such as diarrhea, fever, malaise, and myalgias (see **Special Warnings and Precautions for Use section).** Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis. Hepatotoxicity manifest by elevation of serum alkaline phosphatase, bilirubin, and/or serum transaminases are known to occur following azathioprine use, primarily in allograft recipients. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients. Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of azathioprine tablets. A rare, but life-threatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described in transplant patients and in one patient receiving azathioprine tablets for panuveitis. Periodic measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, azathioprine tablets should be permanently withdrawn.

***Others***
Additional side effects of low frequency have been reported. These include skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis and hepatosplenic T-cell lymphoma (see **Special Warnings and Precautions for Use** section), and Sweet's Syndrome (acute febrile neutrophilic dermatosis).

**Overdose**
The oral $LD_{50}$ for single doses of azathioprine tablets in mice and rats are 2500 mg/kg and 400 mg/kg, respectively. Very large doses of this antimetabolite may lead to marrow hypoplasia, bleeding, infection, and death. About 30% of azathioprine is bound to serum proteins, but approximately 45% is removed during an 8-hour hemodialysis. A single case has been reported of a renal transplant patient who ingested a single dose of 7500 mg azathioprine. The immediate toxic reactions were nausea, vomiting, and diarrhea, followed by mild leukopenia and mild abnormalities in liver function. The white blood cell count, serum glutamic-oxaloacetic transaminase (SGOT), and bilirubin returned to normal 6 days after the overdose.

**PHARMACEUTICAL PARTICULARS**
**Incompatibilities**
None known

**Shelf Life**
Please refer to carton/strip.

**Storage and Precautions**
**Store protected from light. Store below 30°C, protected from moisture**
Keep out of reach of children.

**Special Precautions for Disposal and Other Handling**
Tablet to be swallowed as whole and not to be chewed or crushed.

**Nature and Contents of Container**
10 tablets in a blister. 10 such blisters in a carton.

Marketed by:
**Biocon Biologics India Limited**
Biocon House, Semicon Park,
Electronics City, Phase-II, Bengaluru-560 100, India.

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