Drug Product: AZORAN 50 (Azathioprine Tablets BP 50 mg)

Summary of Product Characteristics

1. Name of the Finished Pharmaceutical Product

AZORAN 50 (Azathioprine Tablets BP 50 mg)

2. Qualitative and Quantitative Composition

Composition:

Each film coated tablet contains:

Azathioprine BP……50 mg

Excipients .....qs.

Sr. No.	Name of Ingredient	Specifications	Quantity (mg/tablet)	Function
Active Ingredient				
1.	Azathioprine	BP	50.000	Active
Excipients				
2.	Lactose Monohydrate (Super tab 30 GR)	BP/ Ph.Eur	70.000	Diluent
3.	Micro Crystalline Cellulose (Avicel PH-102)	BP/ Ph.Eur	29.800	Diluent
4.	Sodium Starch Glycolate (Primojel)	BP/ Ph.Eur	13.000	Disintegrant
5.	Pregelatinized Starch (Starch 1500)	BP/ Ph.Eur	2.000	Binder
6.	Polysorbate 80 (Tween 80)	BP/ Ph.Eur	1.200	Solubilizer
7.	Povidone (K- 30) (Polyvinyl Pyrollidone)	BP/ Ph.Eur	8.000	Binder
8.	Magnesium stearate	BP/ Ph.Eur	1.000	Lubricant
9.	Purified water #	BP/ Ph.Eur	qs	Solvent
Total Core Tablet Weight			**175.000**	
10.	Opadry YS-1R-7006 Clear	Inhouse	3.000	Film coating
11.	Purified Water #	USP/Ph.Eur. /BP/ IP/ IH	q.s	Solvent
Total coated Tablet Weight			**178.00**	

q.s: Quantity Sufficient; BP : British Pharmacopoeia ; Ph. Eur. – European Pharmacopoeia;

USP : United States Pharmacopoeia ; # : Evaporates on drying

3. Pharmaceutical Form:

Film coated tablets.

Pale yellow coloured film coated, round, biconvex, embossed with on one side and breakline on other side.

4. Clinical Particulars:

4.1 Therapeutic indications:

Azathioprine is indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basic immunosuppression).

Azathioprine is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic kidney, liver, heart, lung, or pancreas transplants.

Azathioprine is indicated either alone or in combination with corticosteroids and/or other drugs and procedures in severe cases of the following diseases, in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids:

- Severe active rheumatoid arthritis that cannot be kept under control by less toxic agents (disease modifying anti-rheumatic drugs, DMARDs)
- Severe or moderately severe inflammatory intestinal disease (Crohn's disease or ulcerative colitis)
- Systemic lupus erythematosus
- Dermatomyositis
- Auto-immune chronic active hepatitis
- Polyarteritis nodosa
- Refractory warm auto-immune haemolytic anaemia
- Chronic refractory idiopathic thrombocytopenic purpura

4.2 Posology and method of administration

ROUTE OF ADMINISTRATION: Oral

Posology

Transplantation

Depending on the immunosuppressive regime selected, a dosage of up to 5mg/kg/body weight/day may be given on the first day of therapy. The maintenance dose can range from 1-4 mg/kg/body weight/day and must be adjusted according to the clinical requirements and haematological tolerance.

Other conditions

In general, the starting dosage is 1-3mg/kg/body weight/day and should be adjusted according to the clinical response (which may not be evident for weeks or months) and haematological tolerance.

For the treatment of chronic active hepatitis the dosage is usually between 1.0 and 1.5mg/kg/body weight/day.

When the therapeutic response is evident consideration should be given to reducing the maintenance dosage to the lowest level compatible with maintenance of the response. If no improvement occurs in the patient's condition within three to six months, consideration should be given to withdrawing the medicinal product.

The maintenance dosage required may range from less than 1mg/kg body weight/day to 3mg/kg/body weight/day depending on the clinical condition being treated and the individual patient response including haematological tolerance.

Use in patients with renal and/ or hepatic impairment:

In patients with renal and/ or mild to moderate hepatic dysfunction, dosages should be given at the lower end of the normal range. Azathioprine is contra-indicated in severe hepatic impairment.

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity . These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes. Genotypic testing of NUDT15 variants may be considered before initiating 6-mercaptopurine therapy. In any case, close monitoring of blood counts is necessary.

Paediatric population

There are insufficient data to recommend the use of azathioprine for the treatment of juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis, and polyarteriitis nodosa.

Concerning the other indications the given dose recommendations apply for children and adolescents as well as for adults.

Use in the elderly

There is no specific information on how elderly patients tolerate azathioprine. It is recommended that the dosages used should be at the lower end of the normal range

Combination use

When allopurinol, oxipurinol or thiopurinol is given concomitantly with azathioprine, the dose of azathioprine must be reduced to a quarter of the original dose.

It can take weeks or months before therapeutic effect is seen. The medicinal product may be given over the long term unless the patient cannot tolerate the preparation.

In cases, such as rheumatoid arthritis and certain haematological conditions, the treatment can be stopped after a certain period without problems.

Withdrawal of azathioprine should always be a gradual process performed under close monitoring.

Halving of the film-coated tablet should be avoided unless needed for gradual withdrawal. For appropriate long-term dosing other medicinal products containing 25mg should be used, if necessary.

Method of administration

The film-coated tablets are to be taken orally.

The score line is not intended for the division of tablets into two equal doses and should be swallowed whole with plenty of liquid (at least 200 ml).

The tablets should be taken during meals.

4.3 Contraindications

- Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients
- Severe infections
- Seriously impaired hepatic or bone marrow function
- Pancreatitis
- Any live vaccine, especially BCG, smallpox, yellow fever.
- Pregnancy unless the benefits outweigh the risks
- Lactation

4.4 Special warnings and special precautions for use:

There are potential dangers in the use of azathioprine film-coated tablets; they should therefore not be prescribed unless the patient can be adequately monitored for toxic effects throughout the duration of therapy.

During the first eight weeks of treatment, a complete blood count, including platelet count must be performed at least once weekly. It should be controlled more frequently:

If high doses are used

- In elderly patients
- If renal function is impaired
- If hepatic function is mildly to moderately impaired.
- If bone marrow function is mildly to moderately impaired.
- In patients with hypersplenism

The frequency of the blood count controls may be reduced after 8 weeks. It is recommended that complete blood counts be repeated monthly or at least at intervals of no longer than 3 months.

Patients must be advised to inform their doctor immediately about ulcerations of the throat, fever, infections, bruising, bleeding or other signs of myelosuppression.

Liver function should be controlled regularly, especially in patients with hepatic dysfunction.

Close monitoring of blood counts is required if azathioprine is given together with:

- Allopurinol, oxipurinol or thiopurinol
- Derivatives of aminosalicylic acid, such as mesalazine, olsalazine or sulphasalazine.
- ACE inhibitors, trimethoprim/ sulphamethoxazole, cimetidine or indomethacin .
- Agents with cytotoxic/myelosuppressive properties .

About 10% of patients have thiopurine methyltransferase (TPMT) deficiency due to genetic polymorphism. They may therefore be unable to metabolise azathioprine completely. Consequently they may be exposed to an increased myelotoxic effect. Special care should therefore be taken during co-administration of aminosalicylate derivatives, including sulphasalazine, which are inhibitors of the TPMT enzyme.

Phenotyping or genotyping the patient is desirable, before administration of the medicinal product in order to investigate a possible thiopurine transferase deficiency.

Limited data indicate that azathioprine is not effective in patients with hereditary hypoxanthineguanine-phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome). Therefore azathioprine should not be used in these patients.

If allopurinol, oxipurinol and/or thiopurinol are given concomitantly with azathioprine, the dosage of azathioprine must be reduced to a quarter of the original dose.

Special care is necessary when azathioprine is given concomitantly with neuromuscular acting agents like tubocurarine or succinylcholine. It can also potentiate the neuromuscular block that is produced by depolarising agents such as succinylcholine. Patients should be advised to inform their anaesthesiologist of their treatment with azathioprine prior to surgery.

Coagulation should be closely monitored when anticoagulants of the coumarin type are given concomitantly with azathioprine.

Withdrawal of azathioprine can result in a severe worsening of the condition, e.g. in systemic lupus erythematosus with nephritis, Crohn's disease, ulcerative colitis or autoimmune hepatitis.

Withdrawal of azathioprine should always be a gradual process performed under close monitoring.

If inactivated or toxoid vaccines are applied together with azathioprine, immune response should always be controlled by means of titre determination.

An increased number of skin tumours have occurred in patients during treatment with azathioprine.

They have been mainly on areas of skin exposed to the sun. Patients should be warned about undue exposure to the sun or UV rays, and the skin should be examined at regular intervals.

Particular caution should be exercised in patients with untreated acute infections.

Patients with concomitant cytotoxic therapy may only be given azathioprine under supervision.

Mutagenicity and carcinogenicity/Carcinogenicity

Patients receiving immunosuppressive therapy, including azathioprine are at an increased risk developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities.

A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

Macrophage activation syndrome.

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of azathioprine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with azathioprine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being NUDT15 variant homozygotes. The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10% in East Asians, 4% in Hispanics, 0.2% in Europeans and 0% in Africans. In any case, close monitoring of blood counts is necessary.

Effects on fertility

Relief of chronic renal insufficiency by renal transplantation involving the administration of azathioprine has been accompanied by increased fertility in both male and female transplant recipients

Note for handling the medicinal product:

Azathioprine is mutagenic and potentially carcinogenic. When handling this substance appropriate precautions must be taken. This should be especially considered in pregnant nurses .

If the film-coated tablet has to be halved, contact of the skin with tablet dust or the broken area must be avoided

4.5 Interaction with other FPPs and other forms of interaction

Food, milk and dairy products

The administration of azathioprine with food may decrease systemic exposure slightly but this is unlikely to be of clinical significance (see section 4.8). Therefore, azathioprine may be taken with food

or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme which metabolises 6–mercaptopurine and might therefore lead to reduced plasma concentrations of 6–mercaptopurine .

Vaccines

The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines. It is therefore recommended that patients do not receive live vaccines until at least 3 months after the end of their treatment with azathioprine.

A diminished response to killed vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine and corticosteroids.

A small clinical study has indicated that standard therapeutic doses of azathioprine do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

Effects of concomitant medicinal products on azathioprine

Ribavirin

Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore, co-administration is not advised.

Cytostatic/myelosuppressive agents .

Where possible, concomitant administration of cytostatic agents, or medicinal products which may have a myelosuppressive effect, such as penicillamine, should be avoided. There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and co-trimoxazole.

There have been case reports suggesting that haematological abnormalities may develop due to the concomitant administration of azathioprine and ACE Inhibitors.

It has been suggested that cimetidine and indomethacin may have myelosuppressive effects which may be enhanced by concomitant administration of azathioprine.

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid.

When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6-mercaptopurine or azathioprine, the dose of 6-mercaptopurine and azathioprine should be reduced to 25% of the original dose.

Based on non-clinical data, other xanthine oxidase inhibitors, such as febuxostat, may prolong the activity of azathioprine possibly resulting in enhanced bone marrow suppression. Concomitant

administration is not recommended as data are insufficient to determine an adequate dose reduction of azathioprine.

Aminosalicylate

There is in vitro and in vivo evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme. Therefore, lower doses of azathioprine may need to be considered when administered concomitantly with aminosalicylate derivatives .

Methotrexate

Methotrexate (20 mg/m^2 orally) increased 6-mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m^2 intravenously) increased 6-mercaptopurine AUC by 69 and 93%, respectively.

Infliximab

An interaction has been observed between azathioprine and infliximab. Patients receiving ongoing azathioprine experienced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and a decrease in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after 3 months.

Neuromuscular blocking agents

There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants. Experimental data confirm that azathioprine reverses the neuromuscular blockade produced by non-depolarising agents, and show that azathioprine potentiates the neuromuscular blockade produced by depolarising agents (see section 4.4).

Effect of azathioprine on other drugs

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine; therefore, higher doses of the anticoagulant may be needed. It is

recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with azathioprine.

4.6 Pregnancy and lactation

Fertility

The specific effect of azathioprine therapy on human fertility is unknown.

Pregnancy

Substantial transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the foetus have been shown to occur.

Azathioprine should not be given to patients who are pregnant or likely to become pregnant in the near future without careful assessment of risk versus benefits.

Evidence of the teratogenicity of azathioprine in man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving azathioprine.

Mutagenicity

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the off-spring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with azathioprine.

Azathioprine and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders.

There have been reports of premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure.

Leukopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy.

Breast-feeding

6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Available data has shown that the excreted levels in breast-milk are low. From the limited available data, the risk to newborns/infants is considered to be unlikely but cannot be excluded.
It is recommended that women receiving azathioprine should avoid breast-feeding unless the benefits outweighs the potential risks.
If a decision is made to breastfeed, because 6-mercaptopurine is a strong immunosuppressant, the breastfed infant should be closely monitored for signs of immunosuppression, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis or other symptoms of 6-mercaptopurine exposure.

4.7 Effects on ability to drive and use machines:

Studies on the effects of azathioprine on the ability to drive and use machines have not been performed.

4.8 Undesirable effects:

Undesirable effects are expected to affect about 15% of the patients. The type, frequency and severity of the undesirable effects may depend on the azathioprine dosage, duration of treatment, the patient's underlying condition or any concurrent treatment.

The most important adverse reaction is a dose-related, generally reversible bone marrow depression, most frequently expressed as leucopenia, thrombocytopenia or anaemia. Leucopenia may occur in over 50% of all patients treated with azathioprine in conventional doses. Other signs of bone marrow depression such as thrombocytopenia, anaemia, macrocytosis or megaloblastic bone marrow changes are less frequent.

The adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

	Very common (≥1/10)	Common (≥1/100 to<1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000); including isolated cases	Not Known
Infections and infestations	In 20% of patients with renal homograft (RH)	Increased sensitivity to infection in patients with inflammatory bowel disease.	In <1% of patients with rheumatoid arthritis (RA).			
Neoplasms benign and malignant (including cysts and polyps)		In up to 2.8% of RH-patients (in order of falling frequency): squamous cell skin carcinoma, non-Hodgkin's lymphoma, cervical cancer, Kaposi's sarcoma, vulval cancer.	Post transplantation lymphoproliferative disorder	Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ	Acute myeloid leukaemia and myelo-dysplastic syndrome.	
Blood and lymphatic system disorders	Leucopenia - in >50% with RH (significant in 16%), - in 28% with RA, - in 15% with Crohn's disease	Thrombocytopenia, anaemia. Significant leucopenia in 5.3% of RA patients.		Granulocytopenia, pancytopenia and aplastic anaemia, megaloblastic anaemia, erythro hypoplasia. Agranulocytosis		

Immune system disorders			Hypersensitivity reaction including general malaise, hypotension, dizziness, leukocytosis, exanthema, excessive nausea and vomiting, diarrhoea, fever, shivering, chill, rash, myalgia, arthralgia, vasculitis, renal impairment, elevated hepatic enzymes.		Hypersensitivity reaction with fatal outcome. Stevens-Johnson syndrome and toxic epidermal necrolysis	Acute febrile neutrophilic dermatosis (Sweet's syndrome)
Respiratory, thoracic and mediastinal disorders				Interstitial pneumonia (reversible) .		
Gastrointestinal disorders	Nausea and anorexia with isolated reports of vomiting (12% with RA).	Pancreatitis (0.2-8% most commonly in organ recipients and patients with Crohn's disease.)	Steatorrhoea . Diarrhoea	Gastro-duodenal ulceration, haemorrhage, necrosis or perforation. Colitis, diverticulitis. These complications only occur after transplantation The aetiology is not clearly established. Steroid therapy may be implicated		

Hepatobiliary disorders		Hepatic impairment. Various pathologies including cholestasis, destructive cholangitis, peliosis hepatitis, perisinusoidal fibrosis, and nodular regenerative hyperplasia in 3-10% with RH.	Hepatictoxicity occurs in < 1% of RA-patients.	Life-threatening endophlebitis hepatica obliterans		
Skin and subcutaneous tissue disorders			Alopecia.	Photosensitivity		

Immune system disorders

In cases of hypersensitivity reactions, immediate withdrawal of azathioprine and institution of circulatory support, where appropriate, have led to recovery in the majority of cases. Following a hypersensitivity reaction to azathioprine, the patient must not continue the therapy.

Blood and lymphatic system disorders

TPMT deficiency and impaired hepatic or renal function increase the predisposition for azathioprine-induced bone marrow toxicity.

Even though haemopoiesis is most likely to occur at the start of azathioprine treatment, cases with late onset have been rarely reported. Careful monitoring of the blood counts is recommended, even in patients stabilised on long-term therapy .

Gastrointestinal disorders

Gastrointestinal disorders can be reduced by giving azathioprine in divided doses and/or with meals.

The possibility that exacerbation of diarrhoea might be associated with azathioprine therapy in patients with IBD should be borne in mind.

Hepato-biliary disorders

Endophlebitis obliterans, a rare, but life-threatening disease, has been reported in association with prolonged administration of azathioprine, mainly in transplant recipients. In some cases, the

withdrawal of azathioprine resulted in either a temporary or permanent improvement in liver histology and symptoms.

Cholestasis and deterioration of liver function are usually reversible on withdrawal of therapy.

Neoplasms benign and malignant (including cysts and polyps)

The risk of developing tumours is increased by use of azathioprine both following transplantation and in connection with other indications. The dosage is usually higher for this indication in connection with transplantation. Therefore, the risk of developing tumours is higher when the agent is used in connection with transplantation than with the other indications. The tumour type does not change according to the indication. Typically the tumours occur in connection with immunosuppression (induced by oncovirus or natural irradiation).

Skin and subcutaneous tissue disorders

Hair loss has been described on a number of occasions in patients receiving azathioprine alone or combined with other immunosuppressive agents. In many instances the symptom resolved spontaneously despite continuing therapy.

4.9 Overdose:

Symptoms:

In the event of overdose the most likely effect is bone marrow suppression, reaching its maximum mostly 9-19 days after dosing. The principal signs of bone marrow suppression are ulceration of the throat, fever and infections. Furthermore, bruising, bleeding and fatigue may occur. A single large dose of azathioprine is less likely to have a toxic effect than a chronic minor overdose (e.g. on prescription). Although improvement may be delayed, it usually occurs from the twelfth day after overdose, provided that the patient has not taken a high dose in the meantime.

Treatment:

There is no specific antidote for azathioprine. In the event of overdose, blood count and hepatic function in particular should be monitored. Azathioprine is known to be dialysable and in severe cases dialysis may be used.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutical group: Other immunosuppressive agents;

ATC Code: L04AX01

Azathioprine is used as an immunosuppressive antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) which influence the immune response.

Mechanism of action

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and a methylnitroimidazole moiety. The 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 rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids. Irrespective of whether it is given directly or is derived in vivo from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Determination of plasma concentrations of azathioprine or 6-MP have no prognostic value as regards effectiveness or toxicity of these compounds.

Pharmacodynamic effects

Azathioprine has an effect on both immunological reaction and tumour growth. Its major role has been as an agent for suppressing the immune response. The precise mechanism by which this effect is achieved is not known. However, the following mechanisms of action have been suggested:

i. The action of the released 6-MP as a purine antimetabolite.

ii. The possible blockage of -SH groups by alkylation.

iii. The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of immunocompetent cells (B- and T-lymphocytes).

iv. The damage of deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.

4.1 Pharmacokinetic properties :

Absorption

Azathioprine is well absorbed following oral administration. Although there are no food effect studies with azathioprine, pharmacokinetic studies with 6-mercaptopurine have been conducted that are relevant to azathioprine. The mean relative bioavailability of 6-mercaptopurine was approximately 27% lower following administration with food and milk compared to an overnight fast. 6- mercaptopurine is not stable in milk due to the presence of xanthine oxidase (30% degradation within 30 minutes) (see section 4.2). Azathioprine may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products.

After oral administration of [^{35}S]-azathioprine, the maximum plasma radioactivity occurs at 1-2 hours and decays with a half-life of 4-6 hours. This is not an estimate of the half-life of azathioprine itself, but reflects the elimination from plasma of azathioprine and the [^{35}S]-containing metabolites of the drug. As a consequence of the rapid and extensive metabolism of azathioprine, only a fraction of the radioactivity measured in plasma is comprised of unmetabolised drug. Studies in which the plasma concentration of azathioprine and 6-mercaptopurine have been determined following intravenous administration of azathioprine have estimated the mean plasma T1/2 for azathioprine to be in the range of 6-28 minutes and the mean plasma T1/2 for 6-mercaptopurine to be in the range 38-114 minutes after i.v. administration of the drug.

Azathioprine is principally excreted as 6-thiouric uric acid in the urine. 1-methyl-4-nitro-5-thioimidazole has also been detected in urine as a minor excretory product. This would indicate that, rather than azathioprine being exclusive cleaved by nucleophilic attack at the 5-position of the nitroimidazole ring to generate 6-mercaptopurine and 1-methyl-4-nitro-5-(S-glutathionyl) imidazole. A small proportion of the drug may be cleaved between the S atom and the purine ring. Only a small amount of the dose of azathioprine administered is excreted unmetabolised in the urine.

5.3 Preclinical safety data:

Teratogenicity

Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5-15 mg/kg bodyweight/day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10 mg/kg bodyweight/day.

6. Pharmaceutical Particulars

6.1 List of excipients:

Sr. No	Name of the Ingredient	Specification
1.	Lactose Monohydrate (Super tab 30 GR)	BP/Ph.Eur
2.	Microcrystalline cellulose (Avicel PH-102)	BP/Ph.Eur
3.	Sodium starch glycolate (Primojel)	BP/Ph.Eur
4.	Pregelatinized Starch (Starch 1500)	BP/Ph.Eur
5.	Polysorbate 80 (Tween 80)	BP/Ph.Eur
6.	Povidone (K 30) (Polyvinyl pyrollidone)	BP/Ph.Eur
7.	Magnesium Stearate	BP/Ph.Eur
8.	Opadry YS-1R-7006 Clear	In-house
9.	Purified water	USP/Ph.Eur./BP/ IP/IH

6.2 Incompatibilities

Not applicable

6.3 Shelf life:

36 months from the date of manufacture.

6.4 Special precautions for storage:

Store below 30 °C. Protect from light

6.5 Nature and contents of container:

Alu-PVC/PVDC blister pack of 10 tablets. Such 10 blisters are packed in carton along with pack insert.

7. Marketing authorization holder:

RPG Life Sciences Ltd
RPG House,
463, Dr. Annie Besant Road,
Worli, Mumbai 400 030

Name and address of Manufacture

RPG Life Sciences Limited.

Plot No. 3102-A, G.I.D.C. Estate,
Ankleshwar -393002, Dist. Bharuch,
Gujarat, India

8. Marketing authorization number

CTD19413

9. Date of first authorization/renewal of the authorization

Not applicable

10. Date of revision of the text

31/03/2026