

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Azathioprine Tablets 50mg
Oprisine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains azathioprine 50mg

Excipient(s) with known effect

Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Pale yellow biconvex tablets, scored on one side and engraved with a logo on the other side (mortar and pestle).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azathioprine tablets are used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. Therapeutic effect may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.

Azathioprine tablets, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.

Azathioprine tablets, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

Severe rheumatoid arthritis
Systemic lupus erythematosus
(SLE) Dermatomyositis and
polymyositis Auto-immune

chronic active hepatitis Pemphigus vulgaris
Polyarteritis nodosa
Auto-immune haemolytic anaemia
Chronic refractory idiopathic thrombocytopenic purpura
Pyoderma gangrenosa

4.2 Posology and method of administration

Azathioprine tablets should preferably be taken with or after food.

Transplantation - adults and children

Depending on the immunosuppressive regimen used, a dose of up to 5 mg/kg/day may be given on the first day of therapy.

Maintenance doses should range from 1 to 4 mg/kg/day and must be adjusted according to clinical requirements and haematological tolerance.

Evidence indicates that azathioprine therapy should be maintained indefinitely, even if only low doses are necessary, because of the risk of graft rejection.

Dosage in other conditions - adults and children

In general, the starting dose is from 1 to 3 mg/kg/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerance.

When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing azathioprine.

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

Use in renal or hepatic insufficiency

In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range (see section 4.4 for further details).

Use in the elderly (see Renal and/or hepatic insufficiency)

There is limited experience of the administration of azathioprine to elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with azathioprine, it is recommended that the dosages used should be at the lower end of the range.

Particular care should be taken to monitor haematological response and to reduce the maintenance dosage to the minimum required for clinical response.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to 6-mercaptopurine. Individuals who are hypersensitive to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to Azathioprine Tablets.

Azathioprine therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit (see sections 4.4 and 4.6).

Administration of live vaccines is contraindicated.

4.4 Special warnings and precautions for use

Monitoring

There are potential hazards when using azathioprine and it should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelet counts, should be performed weekly (more frequently if high dosage is used or if severe renal and/or hepatic disorder is present). The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of no longer than 3 months.

Patients receiving azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.

Severe secondary infections, often with uncommon organisms, are a hazard of immunosuppressive therapy. These are seen more frequently in transplant recipients than in patients being treated for other indications.

Individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) may be particularly susceptible to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with azathioprine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. It has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see section 4.8).

Renal and/or hepatic insufficiency

It has been suggested that the toxicity of azathioprine may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion. Nevertheless, it is recommended that the doses used should be at the lower end of the

normal range and that haematological response should be carefully monitored. Doses should be further reduced if haematological toxicity occurs.

Caution is necessary during the administration of azathioprine to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of azathioprine may be impaired, and the dose should therefore be reduced if hepatic or haematological toxicity occurs.

Limited evidence suggests that azathioprine is not beneficial to patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, it is not recommended that these patients should receive azathioprine.

Mutagenicity

Chromosomal abnormalities have been demonstrated in both male and female patients treated with azathioprine. It is difficult to assess the role of azathioprine in the development of these abnormalities.

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.

Carcinogenicity (see section 4.8)

Patients receiving immunosuppressive therapy, including azathioprine are at an increased risk of 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.

Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level.

Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity (see section 4.8).

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.

Pregnancy

Azathioprine should not be initiated in patients who may be pregnant, or who are likely to become pregnant, without careful assessment of risk versus benefit (see section 4.6).

Varicella Zoster Virus Infection (see also section 4.8 Undesirable Effects)

Infection with varicella zoster virus (VZV; chickenpox and herpes zoster) may become severe during the administration of immunosuppressants. Caution should be exercised especially with respect to the following:

Before starting the administration of immunosuppressants, the prescriber should check to see if the patient has a history of VZV. Serologic testing may be useful in determining previous exposure. Patients who have no history of exposure should avoid contact with individuals with chickenpox or herpes zoster. If the patient is exposed to VZV, special care must be taken to avoid patients developing chickenpox or herpes zoster, and passive immunisation with varicella-zoster immunoglobulin (VZIG) may be considered.

If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Withdrawal

Azathioprine may be given long-term unless the patient cannot tolerate the preparation. Withdrawal of an effective dose in certain circumstances, e.g. SLE with nephritis, may result in a serious relapse of the condition. In other instances, such as rheumatoid arthritis and certain haematological conditions, treatment may be withdrawn after a suitable interval without any ill-effect. Withdrawal should always be a gradual process performed under close supervision.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Allopurinol/ oxipurinol/ thiopurinol

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 one-quarter of the original dose.

Neuromuscular blocking agents

Azathioprine can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and can reduce the blockade produced by non-depolarising agents such as tubocurarine. There is considerable variation in the potency of this interaction.

Warfarin

Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine, has been reported.

Cytostatic/myelosuppressive agents

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

Concurrent use of immunosuppressants and ACE inhibitors may lead to an increased risk of haematological reactions such as leucopenia.

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

Other interactions

As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine (see section 4.4).

Furosemide has been shown to impair the metabolism of azathioprine by human hepatic tissue in vitro. The clinical significance is unknown.

Vaccines

The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving azathioprine therapy is contra-indicated on theoretical grounds (see section 4.3).

A diminished response to killed vaccines is likely. This has been observed among patients under treatment with a combination of azathioprine and corticosteroids who have received hepatitis B vaccine.

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.

4.6 Pregnancy and lactation**Teratogenicity**

Azathioprine has caused varying degrees of foetal abnormalities in animal studies (see section 5.3)

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 offspring 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.

Pregnancy

Azathioprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.

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.

Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine.

Leucopenia 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.

4.7 Effects on ability to drive and use machines

No or negligible influence.

4.8 Undesirable effects

There is no currently accepted clinical documentation for azathioprine that can be used to determine the frequency of undesirable effects. Undesirable effects may vary in their incidence and severity depending on the indication; occasionally these adverse effects may have a fatal outcome, particularly in patients receiving several immunosuppressive drugs. The following convention has been utilised for the classification of frequency: Very common, $\geq 1/10$; common, $\geq 1/100$ and $< 1/10$; uncommon, $\geq 1/1000$ and $< 1/100$; rare, $\geq 1/10000$ and $< 1/1000$; very rare, $< 1/10000$.

Infection and infestations

Transplant patients receiving azathioprine in combination with other

immunosuppressants.

Very common: Viral, fungal and bacterial infections

Other indications.

Uncommon: Viral, fungal and bacterial infections

Patients receiving Azathioprine alone, or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection with varicella, herpes zoster and other infectious agents (see also section 4.4 Special Warnings and Precautions for Use).

Neoplasms benign and malignant (including cysts and polyps)

Rare: 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 myelodysplasia (see also section 4.4).

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, is increased in patients who receive immunosuppressive drugs, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself.

There have been rare reports of acute myeloid leukaemia and myelodysplasia (some in association with chromosomal abnormalities).

Blood and lymphatic system disorders

Very common: Bone marrow depression; leucopenia.

Common: Thrombocytopenia.

Uncommon: Anaemia.

Rare: Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.

Azathioprine may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leucopenia, but also sometimes as anaemia and thrombocytopenia, and rarely as agranulocytosis, pancytopenia and aplastic anaemia. These occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy.

Reversible dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and

erythroid hypoplasia is rare.

Respiratory, thoracic and mediastinal disorders

Very rare: Reversible pneumonitis.

Reversible pneumonitis has been described very rarely.

Gastrointestinal disorders

Uncommon: Pancreatitis.

Rare: Colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.

A minority of patients experience nausea when first given azathioprine. This appears to be relieved by administering the tablets after meals.

Serious complications including colitis, diverticulitis and bowel perforation, have been described in transplant recipients receiving immunosuppressive therapy. However, the aetiology is not clearly established and high-dose corticosteroids may be implicated. Severe diarrhoea, recurring on re-challenge, has been reported in patients treated with azathioprine for inflammatory bowel disease. The possibility that exacerbation of symptoms might be drug-related should be borne in mind when treating such patients.

Pancreatitis has been reported in a small percentage of patients receiving azathioprine, particularly in renal transplant patients and those diagnosed as having inflammatory bowel disease. There are difficulties in relating the pancreatitis to the administration of one particular drug, although re-challenge has confirmed an association with azathioprine on occasions.

Hepato-biliary disorders

Uncommon: Cholestasis and abnormal liver function tests.

Rare: Life-threatening hepatic damage.

Cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine therapy and are usually reversible on withdrawal of therapy. This may be associated with symptoms of a hypersensitivity reaction (see Immune system disorders).

Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described primarily in transplant patients. Histological findings include sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. In some cases withdrawal of azathioprine has resulted in either a temporary or permanent improvement in liver histology and symptoms.

Skin and subcutaneous tissue disorders

Rare: Alopecia, photosensitivity.

Hair loss has been described on a number of occasions in patients receiving azathioprine

and other immunosuppressive agents. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is uncertain.

Immune system disorders

Uncommon: Hypersensitivity reactions.

Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis.

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction including interstitial nephritis, hepatic dysfunction and cholestasis (see Hepato-biliary disorders).

In many cases, re-challenge has confirmed an association with azathioprine.

Immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases.

Other marked underlying pathology has contributed to the very rare deaths reported.

Following a hypersensitivity reaction to azathioprine, the necessity for continued administration of the drug should be carefully considered on an individual basis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with azathioprine and result from bone marrow depression which may be maximal after 9 to 14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5 g of azathioprine. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leucopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment

There is no specific antidote. Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. The value of dialysis in patients who have taken an

overdose of azathioprine is not known, although azathioprine is partially dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Immunosuppressive Agents, L04A X01

Azathioprine is an immunosuppressant and antineoplastic agent with similar actions to those of mercaptopurine, to which it is slowly converted in the body.

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 which 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. Determinations of plasma concentrations of azathioprine or 6-MP have no prognostic value as regards effectiveness or toxicity of these compounds.

While the precise modes of action remain to be elucidated, some suggested mechanisms include:

1. the release of 6-MP which acts as a purine antimetabolite.
2. the possible blockade of-SH groups by alkylation.
3. the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.
4. damage to deoxyribonucleic acid (DNA) through incorporation of purine thioanalogues.

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

Azathioprine appears to be well absorbed from the upper gastro-intestinal tract.

Studies in mice with ³⁵S-azathioprine showed no unusually large concentration in any particular tissue, but there was very little ³⁵S found in brain.

Plasma levels of azathioprine and 6-mercaptopurine do not correlate well with the therapeutic efficacy or toxicity of azathioprine.

5.2 Pharmacokinetic properties

Azathioprine is well absorbed following oral administration. 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 $T_{1/2}$ for azathioprine to be in the range of 6-28 minutes and the mean plasma $T_{1/2}$ for 6-MP to be in the range 38-114 minutes after IV 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 exclusively cleaved by nucleophilic attack at the 5-position of the nitroimidazole ring to generate 6-MP 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

Studies in which pregnant rats, mice and rabbits were given azathioprine at doses of 5 to 15 mg/kg/day resulted in varying degrees of foetal abnormalities. Teratogenicity was evident when rabbits were given azathioprine at doses of 10 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Microcrystalline cellulose
Lactose monohydrate
Magnesium stearate
Talc
Sodium starch glycollate (Type A)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in a dry place below 25°C. Protect from light.

6.5 Nature and contents of container

Al/PVC blisters containing 28, 50, 56, 100 and 250 tablets.
Amber PVC tablet container with HDPE snap-cap containing 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

As azathioprine is a cytotoxic drug the tablets should be handled with the precautions normally associated with cytotoxic drugs.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS

8. MARKETING AUTHORISATION NUMBER(S)

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