SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Jayempi 10 mg/ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 10 mg azathioprine.

Excipients with known effect
The suspension contains 1.5 mg sodium benzoate (E211) in each ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

Yellow viscous suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Jayempi 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 in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression).

Jayempi is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and/ or procedures which influence the immune response.

Jayempi is indicated in patients who are intolerant to glucocorticosteroids or if the therapeutic response is inadequate despite treatment with high doses of glucocorticosteroids, in the following diseases:

- severe active rheumatoid arthritis (chronic polyarthritis) that cannot be kept under control by less toxic agents (disease-modifying anti-rheumatic - medicinal products – DMARDs)

- auto-immune hepatitis
- systemic lupus erythematosus
- dermatomyositis
- polyarteritis nodosa
- pemphigus vulgaris and bullous pemphigoid
- Behçet's disease
- refractory auto-immune haemolytic anaemia, caused by warm IgG antibodies
- chronic refractory idiopathic thrombocytopenic purpura

Jayempi is used for the treatment of moderately severe to severe forms of chronic inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis) in patients in whom glucocorticosteroid therapy is necessary, but where glucocorticosteroids are not tolerated, or in whom the disease is untreatable with other common means of first choice.

It is also indicated in adult patients in relapsing multiple sclerosis, if an immunomodulatory therapy is indicated but beta interferon therapy is not possible, or a stable course has been achieved with previous treatment with azathioprine.

Jayempi is indicated for the treatment of generalised myasthenia gravis. Depending on the severity of the disease, Jayempi should be given in combination with glucocorticosteroids because of slow onset of action at the beginning of treatment and the glucocorticosteroid dose should be gradually reduced after several months of treatment.

4.2 Posology and method of administration

Therapy with Jayempi should be initiated by a physician experienced in the administration and monitoring of immunosuppressive medicinal products.

Posology

Transplantation

Depending on the immunosuppressive regime selected, a dose of up to 5 mg/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.

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

Multiple sclerosis (adults only)

The usual dose for the treatment of relapsing forms of multiple sclerosis is between 2 and 3 mg/kg body weight/day.
A treatment duration of more than 1 year may be required until manifestation of the effect, and at least 2 years may be needed until the disease is actually under control.

Myasthenia gravis

The recommended dose for the treatment of myasthenia gravis is 2 mg/kg to 3 mg/kg

body weight/day.
Treatment success usually occurs 2 to 6 months after the start of treatment at the earliest. Depending on the severity of the disease, Jayempi should be given in combination with glucocorticosteroids at the start of treatment because of the slow onset of the effect. The dose of glucocorticosteroids can be gradually reduced over several months.
Treatment with Jayempi should be continued for at least 2 to 3 years.

Chronic active auto-immune hepatitis

The initial dose is usually between 1.0 and 1.5 mg/kg body weight/day and the maintenance dose is up to 2 mg/kg body weight/day.

Dose in other conditions

In general, the starting dose is 1 to 3 mg/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.

When therapeutic response is evident, consideration should be given to reducing the maintenance dose to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 to 6 months, consideration should be given to withdrawing the medicinal product.

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

However, in patients with IBD, a treatment duration of at least 12 months should be considered, whereby a response to treatment may only be recognisable clinically after three to four months.

Interactions with xanthine oxidase inhibitors
With concomitant use of xanthine oxidase inhibitors such as allopurinol, oxipurinol and thiopurinol, the dose of azathioprine should be reduced to a quarter of the normal dose, because allopurinol, oxipurinol and thiopurinol reduce the metabolism of azathioprine (see section 4.5).

The table below shows, for a range of age, weight and doses, the dose (mg) to volume (ml) conversion using the two oral syringes.

Table 1: Dose (mg) to volume (ml) conversion using the two oral syringes

Age (Years)	**Weight* (Kg)**	**Dose†**									
		1mg/kg		**2mg/kg**		**3mg/kg**		**4mg/kg**		**5mg/kg**	
		mg	**ml**	**mg**	**ml**	**mg**	**ml**	**mg**	**ml**	**mg**	**ml**
0	3.3	3.3	0.3	6.6	0.7	9.9	1.0	13.2	1.3	16.5	1.7
1 month	4.5	4.5	0.5	9.0	0.9	13.5	1.4	18.0	1.8	22.5	2.3
2 month	5.6	5.6	0.6	11.2	1.1	16.8	1.7	22.4	2.2	28.0	2.8
3 month	6.4	6.4	0.6	12.8	1.3	19.2	1.9	25.6	2.6	32.0	3.25
4 month	7.0	7.0	0.7	14.0	1.4	21.0	2.1	28.0	2.8	35.0	3.50

5 month	7.5	7.5	0.8	15.0	1.5	22.5	2.3	30.0	3.0	37.5	3.75
6 month	7.9	7.9	0.8	15.8	1.6	23.7	2.4	31.6	3.25	39.5	4.00
1.0	9.6	9.6	1.0	19.2	1.9	28.8	2.9	38.4	3.75	48.0	4.75
1.5	10.9	10.9	1.1	21.8	2.2	32.7	3.25	43.6	4.25	54.5	5.50
2.0	12.2	12.2	1.2	24.4	2.4	36.6	3.75	48.8	5.00	61.0	6.00
3.0	14.3	14.3	1.4	28.6	2.9	42.9	4.25	57.2	5.75	71.5	7.25
4.0	16.3	16.3	1.6	32.6	3.25	48.9	5.00	65.2	6.50	81.5	8.25
5.0	18.3	18.3	1.8	36.6	3.75	54.9	5.50	73.2	7.25	91.5	9.25
6.0	20.5	20.5	2.1	41.0	4.00	61.5	6.25	82.0	8.25	102.5	10.25
7.0	22.9	22.9	2.3	45.8	4.50	68.7	7.00	91.6	9.25	114.5	11.50
8.0	25.4	25.4	2.5	50.8	5.00	76.2	7.50	101.6	10.25	127.0	12.75
9.0	28.1	28.1	2.8	56.2	5.50	84.3	8.50	112.4	11.25	140.5	14.00
10.0	31.2	31.2	3.0	62.4	6.25	93.6	9.25	124.8	12.50	156.0	15.50
12.0	38.2	38.2	3.75	76.4	7.75	114.6	11.50	152.8	15.25	191.0	19.00
15.0	55.5	55.5	5.50	111.0	11.00	166.5	16.75	222.0	22.25	277.5	27.75
18.0	67.0	67.0	6.75	134.0	13.50	201.0	20.00	268.0	26.75	335.0	33.50

*50th percentile for boys extracted from WHO (0-10 years) and UK (11-18 years) growth charts

†Doses less than or equal to 30 mg to be drawn up using the 3 ml oral syringe with 0.1 ml (1mg) graduations. Doses greater than 30 mg to be drawn up using the 10 ml oral syringe with 0.25 ml (2.5mg) graduations (shaded cells).

Special populations

Paediatric population

Transplantation

The posology in paediatric population is the same as in adults.

Myasthenia gravis
The posology in paediatric population is the same as in adults.

Chronic active auto-immune hepatitis
The posology in paediatric population is the same as in adults.

Dose in other conditions
The posology in paediatric population is the same as in adults.

Juvenile idiopathic arthritis
The safety and efficacy of Jayempi in children (0 to 16 years) have not yet been established. No data are available.

Multiple sclerosis
There is no relevant use of Jayempi in the paediatric population for the indication of

multiple sclerosis.

Overweight children

Children considered to be overweight may require doses at the higher end of the dose range. Therefore, close monitoring of response to treatment is recommended (see section 5.2).

Elderly

It is recommended to monitor the kidney and liver function and reduce the dose in the case of impaired function (see section 4.2). The dose used should be at the lower end of the normal range. For controls of blood count, see section 4.4.

Renal and hepatic impairment

In patients with hepatic and/or renal impairment the dose should be reduced to the lower end of the normal range (see section 4.4).

Patients with TPMT deficiency

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe azathioprine toxicity from conventional doses of azathioprine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see sections 4.4 and 5.2).

Most patients with heterozygous TPMT deficiency can tolerate recommended azathioprine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see sections 4.4 and 5.2).

Patients with the NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe azathioprine toxicity (see section 4.4). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes. Genotypic testing of NUDT15 variants may be considered before initiating azathioprine therapy. In any case, close monitoring of blood counts is necessary (see section 4.4).

Method of administration

Jayempi is for oral use and requires redispersing by shaking prior to dosing.

To measure the dose in ml in accordance with the prescribed posology, two oral syringes are included in the pack; 3 ml and 10 ml. The oral syringes are graduated in 0.1 ml (1 mg) and 0.25 ml (2.5 mg) steps respectively.

The healthcare professional should advise the patient or carer which syringe to use to ensure that the correct volume is administered.

In adults without swallowing difficulties, solid oral formulations may be more appropriate and convenient.

Jayempi should be taken at least 1 hour before or 2 hours after a meal or milk.

Water should be taken after each dose in order to ensure accurate and consistent dose delivery to the stomach.

4.3 Contraindications

- Hypersensitivity to the active substance azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients listed in section 6.1.
- Any live vaccine, especially BCG, smallpox, yellow fever (see section 4.5)
- Lactation (see section 4.6).

4.4 Special warnings and precautions for use

Monitoring

Therapy with Jayempi in pre-existing, severe infections, in severe disorders of the liver and bone marrow function and in the presence of pancreatitis should only be initiated subject to a careful benefit/risk analysis and the precautions specified below.

Special attention should be given to monitoring the blood count. If necessary, the maintenance dose should be reduced as much as possible, provided there is clinical response.

Azathioprine should only be prescribed if the patient can be adequately monitored for haematological and hepatic effects throughout the duration of therapy.

During the first 8 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 haematological toxicity occurs, the dose must be reduced (see also sections 4.2 and 5.2)
- if hepatic function is impaired. In this case, liver function should be monitored regularly and if hepatic or haematological toxicity occur, the dose must be reduced (see also sections 4.2 and 5.2).

In particular, patients with impaired liver function require special monitoring when using azathioprine, as life-threatening liver damages have been reported (see section 4.8). This is particularly important in patients with severe impaired liver function and azathioprine should only be used after a careful benefit/risk analysis.

Azathioprine is hepatotoxic, thus regular liver function tests should be repeated during the treatment. More frequent tests are recommended in patients with liver disease and in those who may be undergoing therapy with a possible hepatotoxic adverse reaction. Cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported. Early clinical signs include liver enzyme abnormalities, mild jaundice, thrombocytopenia, and splenomegaly (see section 4.8). The patients should be informed about the symptoms of liver injury and advised to contact their doctor immediately if these occur.

The frequency of blood counts may be reduced after 8 weeks and be repeated monthly or at least at intervals of no longer than 3 months (maximum quarterly).

At the first sign of an abnormal change in the blood count, treatment should be discontinued immediately because the number of leucocytes and platelets may continue to decrease after the end of treatment.

Patients receiving azathioprine must be advised to inform their doctor immediately about any evidence of infection, unexpected bruising or bleeding or other signs of myelosuppression.

Myelosuppression is reversible if azathioprine is discontinued promptly.

Thiopurine methyltransferase (TPMT)

About 10% of patients have decreased activity of the enzyme thiopurine methyltransferase (TPMT) as a result of genetic polymorphism. Especially in homozygous individuals, the degradation of azathioprine is impaired, so there is a higher risk of myelotoxic effects.

This effect can be enhanced by co-administration with medicinal products which inhibit the enzyme TPMT, e.g. olsalazine, mesalazine and sulfasalazine (see section 4.5). Also a possible link between decreased TPMT activity and secondary leukaemia and myelodysplasia has been reported in individual patients receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see section 4.8).

Testing for TPMT deficiency is recommended before treatment, in particular for azathioprine therapy in high doses as well as with rapid deterioration of the blood count.

Patients with the NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk of severe azathioprine toxicity, such as early leucopenia and alopecia, with conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being homozygous carriers of NUDT15 variants (see section 4.2). 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.

Lesch-Nyhan syndrome

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

Varicella zoster virus infection

Infection with varicella zoster virus (VZV; chickenpox and herpes zoster) may become severe during the administration of immunosuppressants (see section 4.8).

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 prevent patients from 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, discontinuation of treatment with azathioprine and supportive care.

Progressive Multifocal Leucoencephalopathy (PML)

PML, an opportunistic infection caused by the JC virus, has been reported in patients receiving azathioprine with other immunosuppressive agents (see section 4.8). Immunosuppressive therapy should be withheld at the first signs or symptoms indicating PML and appropriate evaluation should be undertaken to establish a diagnosis.

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.

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 (UV) light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders.

Carcinogenicity

Patients receiving immunosuppressive therapy, including azathioprine, are at 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 cancers *in situ* (see section 4.8). 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.

There are reports of hepatosplenic T-cell lymphoma in IBD patients who use azathioprine concomitantly with anti-TNF medicinal products.

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

The same as for patients with a high risk of developing skin cancers, 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 minimise the risk of skin cancer and photosensitivity (see also 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 is potentially 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.

Teratogenicity/ contraceptive measures

In preclinical studies azathioprine was mutagenic and teratogenic (see section 5.3). Since there are conflicting findings on the teratogenic potential of azathioprine in humans, contraceptive measures must be taken by both male and female patients of reproductive age during azathioprine therapy for at least six months after the end of azathioprine therapy. This applies also to patients with impaired fertility due to chronic uraemia, since fertility usually returns to normal after transplantation.

Neuromuscular blocking agents

Special caution is required when azathioprine is given concomitantly with neuromuscular blocking agents such as atracurium, rocuronium, cisatracurium or suxamethonium (also known as succinylcholine) (see section 4.5). Anaesthesiologists should check whether their patients are administered azathioprine prior to surgery.

Vaccination

Vaccination with live vaccines can cause infections in immunocompromised patients. Therefore, it is recommended that patients are not administered with any live vaccine until at least 3 months after the end of treatment with azathioprine (see section 4.5).

Metabolic and nutritional disorders

Administration of purine analogues, azathioprine and mercaptopurine, may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Few cases have been reported with the use of azathioprine, especially in patients with IBD (Crohn's disease, colitis ulcerative). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis); gastroenteritis (diarrhoea); or neurologic deficits, including cognitive decline (dementia). Appropriate medical care with niacin/nicotinamide supplementation must be initiated, and dose reduction or discontinuation of azathioprine must be considered.

Ribavirin

Concomitant use of ribavirin and azathioprine is not recommended. Ribavirin can reduce the efficacy of azathioprine and increase the toxicity levels of azathioprine (see section 4.5).

Myelosuppressive agents

The dose should be reduced with concomitant use of azathioprine and myelosuppressive agents.

Posterior reversible encephalopathy syndrome (PRES)

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients using azathioprine. If patients using azathioprine present with symptoms indicating PRES such as headache, altered mental status, seizures, hypertension, and visual disturbances, a diagnostic imaging should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of azathioprine is advised. Most cases reported resolved following discontinuation of azathioprine and appropriate treatment.

Excipients

Sodium benzoate

This medicinal product contains 1.5 mg sodium benzoate in each 1 ml which is equivalent to 300 mg/ 200 ml.

Sodium

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines

The immunosuppressive activity of azathioprine can lead to an atypical and possibly harmful response to live vaccines. Therefore, it is recommended that patients do not receive live vaccines until at least 3 months after the end of treatment with azathioprine (see section 4.4).

Immunosuppressed patients must not be vaccinated with live vaccines, since they are at risk of infection from the live vaccine (see section 4.4).

A decreased immune response to inactivated or toxoid vaccines is likely. This has been observed with hepatitis B vaccine among patients treated with a combination of azathioprine and corticosteroids. Therefore, the vaccination success should always be checked with a titre determination.

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

Effects of concomitantly administered medicinal products on azathioprine

Ribavirin

Ribavirin inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), leading to lower production of active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore, co-administration is not advised (see sections 4.4 and 5.2).

Cytostatic/ myelosuppressive agents

Where possible, concomitant administration of cytostatic medicinal products, or medicinal products which may have a myelosuppressive effect, such as penicillamine, should be avoided (see section 4.4). There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and trimethoprim/sulfamethoxazole.

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 indometacin 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 one quarter of the original dose (see section 4.2). Fatal cases have been reported in patients treated concomitantly with azathioprine and allopurinol.

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 derivatives

There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine and sulfasalazine) inhibit the TPMT enzyme. Therefore, lower doses of azathioprine should be considered when administered concomitantly with aminosalicylate derivatives (see also section 4.4).

Methotrexate

20 mg/m^2 oral methotrexate increased the AUC of 6-mercaptopurine by approximately 31% and 2 or 5 g/m^2 intravenous methotrexate increased the AUC of 6-mercaptopurine by 69% and 93% respectively. Therefore, when azathioprine is administered concomitantly with high-dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

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.

<u>Effects of azathioprine on concomitantly administered medicinal products</u>

Anticoagulants

A reduction of the anticoagulant effect of warfarin was described following the simultaneous use of azathioprine.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Malformations occurred in animal experiments due to azathioprine. In animal studies azathioprine was teratogenic and embryotoxic (see section 5.3). There are conflicting findings on the teratogenic potential of azathioprine in humans. Azathioprine must only be used during pregnancy after a careful benefit/risk analysis.

Both male and female patients of reproductive age should use contraceptive methods while using azathioprine. Men should not father children during and up to 6 months after the end of treatment. This also applies to patients with reduced fertility due to chronic uraemia, as fertility generally returns to normal after a transplant.

It is known that considerable amounts of azathioprine and its metabolites pass through the placenta and amniotic sac, and are thereby transferred from the mother to the foetus.

Blood count changes (leucopenia and/or thrombocytopenia) have been reported in a number of neonates whose mothers received azathioprine during pregnancy. Extra care in haematological monitoring of the mother is advised during pregnancy.

Temporary impairment of the immune response was detected in neonates from intrauterine exposure to a combination of azathioprine with prednisone. There have been reports of intrauterine growth retardation, premature births and low birth weights vis-à-vis azathioprine, in particular in combination with corticosteroids. Moreover, data is available on spontaneous abortions after both maternal and paternal exposure.

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes of 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.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy. Early diagnosis and discontinuation of azathioprine may minimise impact on the foetus. However, a careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed.

Breast-feeding

6-Mercaptopurine, the active metabolite of azathioprine, has been identified in the colostrum and breast milk of women receiving azathioprine treatment. Breast-feeding

and concomitant use of azathioprine are contra-indicated (see section 4.3). If treatment with azathioprine is unavoidable, breast-feeding should be discontinued.

Fertility

No preclinical or clinical data is available on the possible influence of azathioprine on male and female fertility (see section 4.4).

4.7 Effects on ability to drive and use machines

Jayempi has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most important adverse reactions include bone marrow depression, most frequently expressed as leukopenia and thrombocytopenia; viral, fungal and bacterial infections; life-threatening liver injury; hypersensitivity, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Tabulated list of adverse reactions

The adverse reactions are listed below according to system organ class and frequency. The frequencies are defined as follows: 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) (including isolated cases), not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Infections and infestations	Very common	Viral, fungal and bacterial infections (in transplant recipients who are treated with azathioprine in combination with other immune-suppressants)
	Uncommon	Viral, fungal and bacterial infections (in other patients)
	Very rare	Cases of progressive multifocal leukoencephalopathy (PML) caused by the JC virus have been reported after using azathioprine in combination with other immunosuppressants (see section 4.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (malignant melanomas and non- melanomas), sarcomas (Kaposi's and non-Kaposi's), uterine cancer, cervix carcinoma, acute

System organ class	Frequency	Adverse reactions
		myeloid leukaemia and myelodysplastic syndrome (see also section 4.4)
	Very rare	Hepatosplenic T-cell lymphoma (in IBD patients using other anti-TNF drugs concomitantly)
Blood and lymphatic system disorders	Very common	Leukopenia, bone marrow depression
	Common	Thrombocytopenia
	Uncommon	Anaemia
	Rare	Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia and erythroid hypoplasia
	Very rare	Haemolytic anaemia
Immune system disorders	Uncommon	Hypersensitivity
	Very rare	Stevens-Johnson syndrome and toxic epidermal necrolysis
Metabolism and nutrition disorders	Not known	Pellagra (see section 4.4)
Nervous system disorders	Not known	Posterior reversible encephalopathy syndrome (PRES), tremor
Respiratory, thoracic and mediastinal disorders	Very rare	Pneumonitis (reversible)
Gastrointestinal disorders	Common	Nausea, vomiting
	Uncommon	Pancreatitis
	Very rare	Colitis, diverticulitis and intestinal perforation in transplant recipients, diarrhoea (severe) in patients with inflammatory bowel disease
	Not known	Sialoadenitis
Hepatobiliary disorders	Uncommon	Cholestasis and cholestasis of pregnancy
	Rare	Liver injury
	Not known	Non-cirrhotic portal hypertension, portosinusoidal vascular disease
Skin and subcutaneous tissue disorders	Rare	Alopecia
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), photosensitivity reaction
Investigations	Uncommon	Liver function test abnormal
Renal and urinary disorders	Not known	Chromaturia

Description of selected adverse reactions

Infections and infestations

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 infections with varicella, herpes zoster and other infectious pathogens (see section 4.4).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

The risk of developing non-Hodgkin's lymphoma 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 immunosuppressants, particularly in transplant patients receiving aggressive treatment, and such therapy should be maintained at the lowest effective levels (see section 4.4). 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 leucaemia and myelodysplasia (some in association with chromosomal abnormalities).

Blood and lymphatic system disorders

The most common adverse reaction of azathioprine is a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leucopenia, but also sometimes as thrombocytopenia and anaemia, and rarely as agranulocytosis, pancytopenia and aplastic anaemia.

These occur particularly in patients predisposed to myelosuppression, such as those with TPMT deficiency and renal or hepatic impairment and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy (see sections 4.2 and 4.5).

Reversible, dose-related macrocytosis and increase in 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 are rare.

Immune system disorders

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, erythema nodosum, vasculitis, myalgia, arthralgia, hypotension, cardiac dysfunction, renal dysfunction, hepatic dysfunction and cholestasis. In many cases, re-challenge has confirmed an association with azathioprine.

Hypersensitivity reactions and other marked underlying pathology may have contributed to the very rare deaths reported.

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 necessity for continued administration of azathioprine should be carefully considered on an individual basis.

Gastrointestinal disorders

Gastrointestinal disorders occur primarily in the form of nausea after taking oral azathioprine.

A small number of patients experience nausea when first given azathioprine. To reduce nausea, the dose should be taken after a meal.

Pancreatitis has been reported in patients on azathioprine therapy, particularly in renal transplant patients and those diagnosed as having inflammatory bowel disease. It is

difficult to attribute pancreatitis to the administration of one particular medicinal product, although re-challenge has confirmed an association with azathioprine in some instances.

Serious complications, including colitis, diverticulitis and bowel perforation, have been reported in transplant patients receiving immunosuppressive therapy. However, the causal relationship is not clearly established and high-dose corticosteroids may be implicated.

Severe diarrhoea, recurring on re-exposure, has been reported in patients with inflammatory bowel disease treated with azathioprine. If there is any exacerbation of symptoms in these patients, a possible causal relationship with the azathioprine treatment should be taken into consideration.

Hepatobiliary disorders

Dose-dependent cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine therapy and are usually reversible on discontinuation of therapy. This may be associated with features of a hypersensitivity reaction.

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

Skin and subcutaneous tissue disorders

Alopecia has been described for both monotherapy and combined therapy with azathioprine. In many instances, the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is still unclear.

Renal and urinary disorders

A minority of patients receiving azathioprine develop chromaturia, often presenting as bright yellow urine. Chromaturia may occur independent of, or because of, renal or hepatic disorder. Other urine discolourations or darkening are indicative of an underlying renal or hepatic pathology and may require investigation.

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The most common effect of overdose with azathioprine is myelosuppression with

blood count disorders, which may be maximal after 9 to 14 days. The main symptoms of myelosuppression are mouth and throat ulceration, bruising, fever of unknown aetiology and unexplained infection.
Furthermore, spontaneous bleeding and extreme fatigue may occur. These symptoms are more likely to present following prolonged mild overdose, rather than after a single acute overdose.
A case of a patient who ingested a single dose of 7.5 g azathioprine has been reported. Acute symptoms included nausea, vomiting and diarrhoea, followed by moderate leucopenia and mild impairment of the liver function. Recovery was without sequelae.

Management

Since there is no specific antidote, the blood count should be closely monitored, appropriate symptomatic treatment should be initiated, where necessary, and the appropriate blood transfusions be administered.
In the case of overdose, active measures (such as use of activated charcoal) will probably only be effective if they are carried out within 60 minutes of ingestion.

Azathioprine is partially dialysable. Nevertheless, the benefit of dialysis in patients who have taken an overdose is not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Other immunosuppressants,
ATC code: L04AX01

Mechanism of action

Azathioprine is an inactive pro-drug of 6-mercaptopurine (6-MP), which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for immunosuppression. TGNs and other metabolites (e.g. 6-methylmercaptopurine ribonucleotides) inhibit *de novo* purine synthesis and purine nucleotide interconversions. The TGNs are also incorporated into nucleic acids and this contributes to the immunosuppressive effects of the medicinal product.
Other potential mechanisms of azathioprine include:

- The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of cells involved in the immune response (B and T lymphocytes).

Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment (see section 4.2).
Unlike 6-MP, the activity of the azathioprine metabolite 1-methyl-4-nitro-5-thioimidazole has not been clearly determined. However, compared with 6-MP it appears to modify the activity of azathioprine in several systems.

In a controlled study in patients with myasthenia gravis, azathioprine (2.5 mg/kg body

weight/day) in combination with prednisolone proved to be significantly better in comparison to prednisolone and placebo in terms of treatment failure. Furthermore, a glucocorticosteroid-sparing effect was seen after 15 months. After 36 months, 63% in the azathioprine group required no further glucocorticosteroids, compared with only 20% in the placebo group.

5.2 Pharmacokinetic properties

Absorption

Azathioprine is incompletely and variably absorbed. The mean absolute bioavailability of 6-MP after administration of azathioprine 50 mg is 47% (range: 27-80%). The extent of absorption of azathioprine is similar throughout the gastrointestinal tract, including the stomach, jejunum and caecum. The extent of 6-MP absorption after application of azathioprine however, varies depending on where the absorption occurs, with the highest level in the jejunum, followed by the stomach and caecum.

In a comparative bioavailability study in healthy adult volunteers (n=29), 50 mg of azathioprine oral suspension was demonstrated to be bioequivalent to the reference 50 mg tablet for AUC, but not C_{max}. The mean (90% CI) C_{max} with the oral suspension was 12% (93% - 135%) higher than the tablet although the range of C_{max} observations was more or less the same for the oral suspension and tablet; 5.7 – 40.0 and 4.4 – 39.5 ng/ml, respectively.

Although interactions with food were not studied, pharmacokinetic studies with 6-mercaptopurine have been conducted that are relevant to azathioprine. The mean relative bioavailability of 6-mercaptopurine was approximately 26% lower after administration with food and milk compared to after fasting.
6-mercaptopurine is not stable in milk due to the presence of xanthine oxidase (30% degradation within 30 minutes) (see “Biotransformation”). Azathioprine should be taken at least 1 hour before or 2 hours after a meal or milk (see section 4.2).

There is no correlation between the plasma concentrations of azathioprine and 6-mercaptopurine and the therapeutic efficacy or toxicity of azathioprine.

Distribution

Azathioprine is rapidly distributed in the body. The steady-state volume of distribution (Vdss) of azathioprine is unknown. The mean (± SD) apparent Vdss of 6-MP is 0.9 (± 0.8) l/kg, although this value is probably too low, since 6-MP is metabolised throughout the body and not just in the liver.
Approximately 30% of azathioprine is bound to plasma proteins.

Azathioprine and its metabolites pass through the central nervous system. 6-MP concentration in the cerebrospinal fluid are low or negligible after intravenous or oral use.

Biotransformation

Azathioprine is rapidly metabolised *in vivo* by glutathione S-transferase into the

metabolites 6-MP and 1-methyl-4-nitro-5-thioimidazole. 6-MP passes cell membranes rapidly and is extensively metabolised in numerous multistep metabolic processes into active and inactive metabolites without any enzyme being predominantly active. Due to the complex metabolism, all cases of non-efficacy and/or myelosuppression cannot be explained by the inhibition of a single enzyme. The enzymes mainly responsible for the metabolism of 6-MP and its metabolites are the polymorphic enzyme thiopurine methyltransferase (TPMT) (see sections 4.4 and 4.5), xanthine oxidase (see sections 4.5 and 5.2), inosine monophosphate dehydrogenase (IMPDH) (see section 4.5) and hypoxanthine-guanine phosphoribosyltransferase (HPRT). Other enzymes involved in the formation of active and inactive metabolites are guanosine monophosphate synthetase (GMPS, which forms TGNs) and inosine triphosphate pyrophosphatase (ITPase).
Azathioprine is also metabolised by aldehyde oxidase to the probably active 8-hydroxy-azathioprine. Furthermore, various inactive metabolites are also formed in further metabolic processes.

There are indications that polymorphisms in the genes which encode the various enzyme systems involved in the metabolism of azathioprine may predict adverse reactions in azathioprine therapy.

Thiopurine methyl transferase (TPMT)

TPMT activity is inversely related to red blood cell 6-mercaptopurine-derived thioguanine nucleotide concentration, with higher thioguanine nucleotide concentrations resulting in greater reductions in white blood cell and neutrophil counts. Individuals with TPMT deficiency develop very high cytotoxic TGN concentrations.

Genotypic testing can determine a patient's allelic pattern. Currently, 3 alleles – TPMT*2, TPMT*3A and TPMT*3C – account for 95% of individuals with reduced levels of TPMT activity.
Approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity, whereas 90% of individuals have normal TPMT activity with two functional alleles. For a group of about 2% it can also lead to very high TPMT activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells and can further provide other information (see section 4.4).

<u>Elimination</u>

The plasma half-life is 3 to 5 hours. After oral administration of 100 mg ^{35}S-azathioprine, 50% of the radioactivity is excreted in the urine within 24 hours and 12% in the faeces within 48 hours. The main component in the urine was the inactive oxidized metabolite thiourea. Less than 2% was excreted in urine, in the form of azathioprine or 6-MP. In healthy subjects, azathioprine is eliminated rapidly with a total clearance greater than 3 L/min. There are no data available on the renal elimination or half-life of azathioprine. The renal clearance of 6-MP and half-life of 6-MP are 191 ml/min/m^2 and 0.9 hours respectively.

6-mercaptopurine has been detected in the colostrum and breast milk of women who were treated with azathioprine (6-mercaptopurine is excreted in breast milk at concentrations of 3.4 ng/ml to 18 ng/ml).

Special populations

Elderly patients

No specific studies have been carried out in the elderly (see section 4.2).

Overweight children

In a clinical trial in the United States, 18 children between the ages of 3 and 14 were evenly split into two groups; the crucial factor was whether the ratio of weight to height was greater or less than the 75th percentile. Each child was undergoing maintenance treatment with 6-MP, whereby the body surface was the basis for the dose calculation. The mean AUC (0-∞) of 6-MP in the group greater than the 75th percentile was 2.4 times smaller than that in the group less than the 75th percentile. Therefore, under certain circumstances, overweight children need azathioprine doses in the upper range of the dose spectrum, and close monitoring of their response to treatment (see section 4.2).

Renal impairment

Studies with azathioprine showed no difference in the pharmacokinetics of 6-MP in uraemic patients compared with patients with a kidney transplant. Since little is known about the active metabolites of azathioprine in renal dysfunction, a dose reduction in patients with impaired renal function should be considered (see section 4.2).

Azathioprine and/or its metabolites are removed by haemodialysis, with approximately 45% of the radioactive metabolites being removed during an 8-hour dialysis session.

Hepatic impairment

In case of hepatic impairment, the metabolism of azathioprine is altered. Conversion into the active metabolites is restricted. However, the elimination of metabolites is reduced (see sections 4.2 and 4.4).

An azathioprine study was carried out on a group of kidney transplant patients. They were split into three groups: patients with no liver disease, patients with hepatic dysfunction (but with no cirrhosis) and patients with hepatic dysfunction and cirrhosis. The study showed that the 6-mercaptopurine level was 1.6 times higher in patients with hepatic dysfunction (but with no cirrhosis) and 6 times higher in patients with hepatic dysfunction and cirrhosis, compared with patients with no liver disease. Therefore, a dose reduction should be considered in the case of patients with impaired liver function (see section 4.2).

5.3 Preclinical safety data

Reproductive toxicity

In embryotoxicity studies azathioprine showed teratogenicity or embryo lethality in various animal species. In rabbits, a dose of 5-15 mg/kg body weight/day produced

skeletal abnormalities. In mice and rats, doses of 1-2 mg/kg body weight/day were lethal to embryos.

Mutagenicity

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

Carcinogenicity

In long-term carcinogenicity studies of azathioprine in mice and rats receiving doses that were up to 2-fold the human therapeutic dose and in lower doses administered in immuno-compromised mice, an increased incidence of lymphosarcomas (mice) and squamous cell tumours and carcinomas (rats) were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)
Sucralose (E955)
Banana flavour
Citric acid monohydrate
Microcrystalline cellulose and carmellose sodium
Xanthan gum
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After first opening: 12 weeks

6.4 Special precautions for storage

Do not store above 25°C.

Keep the bottle tightly closed (see section 6.6).

6.5 Nature and contents of container

Amber type III glass bottle with tamper evident child-resistant closure (HDPE with expanded polyethylene liner) containing 200 ml of oral suspension.

Each pack contains one bottle, an LDPE bottle adaptor, a 3 mL oral dosing syringe (0.1 mL dose graduations) and a 10 mL oral dosing syringe (0.25 mL dose graduations).

6.6 Special precautions for disposal

Anyone handling Jayempi should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling Jayempi.

Contact with skin or mucous membrane must be avoided. If Jayempi comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water. Spillages must be wiped immediately.

Women who are pregnant, planning to be or breast-feeding should not handle Jayempi.

Parents / care givers and patients should be advised to keep Jayempi out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Keep the bottle tightly closed to protect the integrity of the medicinal product and minimise the risk of accidental spillage.
The bottle should be shaken to ensure the oral suspension is well mixed.

Disposal

Jayempi is cytotoxic. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Wigston, Leicester

LE18 4YL

United Kingdom

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