SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azathioprine 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg azathioprine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light yellow, round, biconvex tablet, engraved “AZA” and “50” separated by a line on one side and plain on the 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

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. (See section 4.3).

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity (see section 4.4). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes (see section 4.4). 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 (for controls of blood count see section 4.4).

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 (see sections 4.4 and 4.5).

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 (see sections 4.4 and 6.6). For appropriate long-term dosing other medicinal products containing 25mg should be used, if necessary.

Method of administration

For oral use.

The tablet should be taken with at least a glass of liquid (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 listed in section 6.1.
- 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 (see section 4.6)
- Lactation (See section 4.6)

4.4 Special warnings and 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 (see also sections 4.2 and 5.2)
- If bone marrow function is mildly to moderately impaired (see also section 4.2)
- 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 (see sections 4.2 and 4.5)
- Derivatives of aminosalicylic acid, such as mesalazine, olsalazine or sulphasalazine (see section 4.5)
- ACE inhibitors, trimethoprim/ sulphamethoxazole, cimetidine or indomethacin (see section 4.5)
- Agents with cytotoxic/myelosuppressive properties (see section 4.5)

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 (see section 4.2 and 4.5).

Neuromuscular blocking agents

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

Coagulation should be closely monitored when anticoagulants of the coumarin type are given concomitantly with azathioprine (see section 4.5).

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 (see also section 4.8).

Particular caution should be exercised in patients with untreated acute infections (see also section 4.3).

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 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.

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 (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.

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 (for contraceptive measures see section 4.6).

Excipient

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

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 (see section 6.6).

If the film-coated tablet has to be halved, contact of the skin with tablet dust or the broken area must be avoided (see section 4.2 and 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

Allopurinol, oxipurinol and thiopurinol have an inhibitory effect on the metabolism of azathioprine by blocking the enzyme xanthinoxidase. If allopurinol, oxipurinol and/or thiopurinol are administered concomitantly with azathioprine, the dose of azathioprine must be reduced to a quarter of the original dose (see sections 4.2 and 4.4).

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.

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).

If azathioprine is combined with other immunosuppressants, such as cyclosporin or tacrolimus, the greater risk of excessive immunosuppression must be taken into consideration.

Interactions have been observed between azathioprine and infliximab in treatment of Crohn’s disease.
Patients receiving on-going azathioprine experienced transient increases in 6-TGN levels (6-thioguanine nucleotide, an active metabolite of azathioprine) and decreases in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after 3 months.

There is a risk of an increased myelosuppressive effect of azathioprine, as a result of inhibition of its hepatic metabolism, if azathioprine is administered concomitantly

with aminosalicylate derivatives such as olsalazine, mesalazine and sulfasalazine, (See section 4.4).

Inhibition of the anticoagulant effect of warfarin and phenprocoumon, has been reported if administered concomitantly with azathioprine (see section 4.4).

Concomitant therapy with azathioprine and ACE-inhibitors, trimethoprim/sulpfamethoxazole, cimetidine or indomethacin increases the risk of myelosuppression (see section 4.4).

Concomitant therapy with azathioprine and agents with myelosuppressive/cytotoxic properties may enhance the myelotoxic effects. This applies also to myelosuppressive therapies completed only shortly before initiation of treatment with azathioprine (see section 4.4).

It has been shown that furosemide reduces the metabolism of azathioprine by human hepatic tissue *in vitro*. The clinical relevance of this is not known.

The immunosuppressive activity of azathioprine can lead to an atypical and possibly harmful response to live vaccines, and therefore, for theoretical reasons, the administration of live vaccines to patients being treated with azathioprine is contraindicated (see section 4.3).

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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Azathioprine must not be used during pregnancy without careful assessment of risks and benefit (see section 4.3).
In animal studies Azathioprine was teratogenic and embryotoxic (see section 5.3).
Azathioprine and its metabolites have been found in low concentrations in foetal blood and amniotic fluid after administration to the mother. 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 and a dose reduction in case of leucopenia is advised during pregnancy.

After *in utero* exposure to azathioprine in combination with prednisone, a temporary reduction of immune function is observed. Intra-uterine growth retardation and premature birth have been reported in cases of treatment with azathioprine together with prednisolone. The long-term consequences of these properties of azathioprine are not known, but many children exposed to the substance *in utero* have now reached the age of ten years without any problems being reported.

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).

Fertility
Contraceptive measures must be taken by both male and female patients of reproductive age during, and for at least three months after the end of azathioprine therapy.
This applies also to patients with impaired fertility due to chronic uraemia, since that usually returns to normal after transplantation.

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		In up to 2.8% of RH patients (in	Post-transplantation	Neoplasms including lymphoprolif	Acute myeloid leukaemia	

(including cysts and polyps)		order of falling frequency): squamous cell skin carcinoma, non-Hodgkin’s lymphoma, cervical cancer, Kaposi’s sarcoma, vulval cancer.	lymphoproliferative disorder.	erative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ (see section 4.4).	and myelodysplastic 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, erythrohypoplasia, Agranulocytosis		
Immune system disorders			Hypersensitivity reaction including general malaise, hypotension, dizziness, leukocytosis, exanthema, excessive nausea and vomiting, diarrhoea, fever, shivering, chill, rash, erythema nodosum, myalgia, arthralgia, vasculitis, renal impairment, elevated hepatic enzymes.		Hypersensitivity reaction with fatal outcome. Stevens-Johnson syndrome and toxic epidermal necrolysis	
Respiratory, thoracic and				Interstitial pneumonia		

mediastinal disorders				(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.	Gastroduodenal 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.	Hepatic toxicity occurs in < 1% of RA patients.	Life-threatening endophlebitis hepatica obliterans.		
Skin and subcutaneous tissue disorders			Alopecia.	Photosensitivity		Acute febrile neutrophilic dermatosis (Sweet's syndrome)

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 (see section 4.4).

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.

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:

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 1-methyl-4-nitro-5-thioimidazole.

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 activity of the methylnitroimidazole moiety has not been defined clearly. However, in various systems it appears to modify the activity of azathioprine compared with that of 6-MP.

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.

5.2 Pharmacokinetic properties

Absorption

Azathioprine is well absorbed following oral administration. Peak plasma concentrations are reached 1-2 hours after taking a dose.

Distribution

Azathioprine is distributed rapidly throughout the body. The plasma half life is 3-5 hours. Only 30% of the medicinal product binds to plasma proteins. 12.5% enter the cerebrospinal fluid.

Biotransformation

Azathioprine is extensively metabolised to 6-thioinosinic acid and methyl mercaptopurine-ribonucleotide, which, in part, are responsible for the effect of the medicinal product.

The effect *in-vivo* is complicated by the action of methyl-nitroimidazole, which is also found.

Elimination

Up to 50% of a dose is excreted in urine during the first 24 hours after administration, with approximately 10% as unchanged substance. Only 12.6% of the dose is excreted during 48 hours with the faeces. There is no evidence for enterohepatic circulation.

A lowered dosage for patients with reduced renal function may be necessary, probably as a result of reduced elimination of the active metabolites of azathioprine.

Also in patients with hepatic impairment the metabolism of azathioprine is altered. Conversion into the active form is reduced, and especially the breakdown to eliminable metabolites is diminished (see sections 4.2 and 4.4).

Mercaptopurine, a metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

5.3 Preclinical safety data

Teratogenicity or embryolethality has been seen in a number of animal species with varying degree of susceptibility. In rabbits, a dose of 5-15 mg/kg body weight daily

on days 6-14 of pregnancy produced skeletal abnormalities, in mice and rats, doses of 1-2 mg/kg body weight daily on days 3-12 were lethal to embryos.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose.

Mannitol.

Maize starch.

Povidone K25.

Croscarmellose sodium.

Sodium stearyl fumarate.

Tablet coat:

Hypromellose,

Macorogol 400.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light

6.5 Nature and contents of container

PVC/PVDC/aluminium blister packaging.

50, 56 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

There are no risks associated with handling tablets with intact coating. In that case no special safety precautions are necessary.

However, cytotoxic agents should be handled in strict accordance with the instructions when nursing staff have halved the tablets (see sections 4.2 and 4.4).

Surplus medical products as well as contaminated appliances should be temporarily stored in clearly labelled containers. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Resolution Chemicals Ltd.,

Wedgwood Way,

Stevenage, Herts,

SG1 4QT, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 10321/0214

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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18/08/2021