SUMMARY OF PRODUCT CHARACTERISTICS

Azathioprine AqVida 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Azathioprine AqVida 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 50 mg Azathioprine.

1 film-coated tablet contains 68.72 mg – 70.50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Pale yellow coloured, film-coated, round, biconvex tablets, embossed "AZ50" on the one side and a score mark on the reverse.

The tablet can be divided into equal doses.

Thickness limit (3.0 – 3.6 mm)
Diameter : 8.0 mm

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 (basis 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 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 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 diseases (Crohn's disease or ulcerative colitis)
- systemic lupus erythematosus

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Formatiert: Englisch (Großbritannien)

- dermatomyositis and polymyositis
- auto-immune chronic active hepatitis
- polyarteritis nodosa
- auto-immune haemolytic anaemia
- chronic refractory idiopathic thrombocytopenic purpura

4.2 Posology and method of administration

Posology

Transplantation
Depending on the immunosuppressive regimen selected, a dosage 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 per 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.

Other conditions
In general, the starting dosage is 1-3 mg/kg body weight/day, and should be adjusted according to the clinical response (which may be evident only after weeks or months) and haematological tolerance.
When the therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the 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 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.

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

Use in patients with renal and/or hepatic impairment
In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range. Azathioprine is contraindicated in severe hepatic impairment (see section 4.3)

Use in Children and Adolescents
There are insufficient data to recommend the use of azathioprine for the treatment of juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis and polyarteritis 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).

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 section 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.

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

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

The tablet can be divided into the equal doses. If splitting of the tablets might be necessary, avoid skin contamination and inhalation of tablet particles (see sections 4.4 and 6.6). Crushing of the tablets should be avoided. For appropriate long-term dosing, the 25 mg strength (Azathioprine AqVida 25 mg film-coated tablets) should be used.

Method of administration
For oral use.
The tablet(s) should be taken with at least a glass of liquid (200ml).
The tablet(s) should be taken during meals in order to decrease the risk of nausea.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypersensitivity to 6-mercaptopurine (metabolite of azathioprine)
- 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; 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 counts, 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 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 not 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.

- Especially in patients with hepatic dysfunction, liver function should be controlled regularly.

- There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive 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. Also 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).

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

- 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.

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

- Withdrawal of azathioprinecan result in a severe worsening of the condition, e.g. in systemic lupus erythematosus with nephritis, dermatomyositis and polymyositis; Crohn's disease, ulcerative colitis; polyarteritis nodosa; chronic refractory idiopathic thrombocytopenic purpura; auto-immune haemolytic anaemia; severe active rheumatoid arthritis 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 AqVida, 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 to 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 AqVida under supervision.

Progressive multifocal leukoencephalopathy (PML)
PML, an opportunistic infection caused by the JC virus, has been reported in patients treated with azathioprine at the same time as other immunosuppressants. The immunosuppressive therapy should be discontinued as soon as any signs or symptoms suggestive of PML develop, and an appropriate evaluation should be undertaken to establish a diagnosis (see section 4.8).

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.

Carcinogenicity (see also 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.
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).

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

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

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.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

- 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).

- There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants such as curare, d-tubocurarine and pancuronium. Experimental data confirm that azathioprine reverses the neuromuscular blockade produced by d-tubocurarine, and show that azathioprine potentiates the neuromuscular blockade produced by succinylcholine (see section 4.4). Patients should be advised to inform their anaesthesiologist of their treatment with azathioprine prior to surgery.

- 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 ongoing 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 aminosalicylic acid derivatives such as olsalazine, mesalazine and sulphasalazine (see section 4.4).

- Inhibition of the anticoagulant effect of warfarin and phenprocoumon, has been reported if administered concomitantly with azathioprine, therefore coagulation should be closely monitored (see section 4.4).

- Concomitant therapy with azathioprine and ACE inhibitors, trimethoprim/sulphamethoxazole, cimetidine or indomethacin increase 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 reduced the metabolism of azathioprine by human hepatic tissue *in vitro*. The clinical relevance 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

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration (see section 4.4).

- An oral dose of 20 mg/m^2 increased the AUC of 6-mercaptopurine by about 31%, while an intravenous administration of 2 and 5 g/m^2 methotrexate, respectively, increased the AUC of 6-mercaptopurine by 69 and 93%, respectively. Therefore, in case of concomitant application of high doses of methotrexate, the azathioprine dose should be adjusted to keep the number of white blood cells at an adequate value.

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.
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. Azathioprine has been reported to interfere with the effectiveness of intrauterine contraceptive devices. Therefore it is recommended to use other or additional contraceptive measures.

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
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 above).

4.7 Effects on ability to drive and use machines

Due to the possibility of adverse drug reactions such as dizziness, and because of individually occurring different reactions, the ability to participate actively in traffic or operate machines may be influenced adversely by azathioprine treatment. This is to be considered especially in combination with alcohol.

4.8 Undesirable effects

Approximately 15 % of patients can be expected to experience undesirable effects. The type, frequency and severity of adverse reactions may depend on the dose of azathioprine and duration of therapy as well as on the patient's underlying disease or concomitant therapies.

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

The principal undesirable effect of azathioprine is a dose-related, generally reversible depression of bone marrow function expressed as leucopenia, thrombocytopenia and anaemia. Leucopenia may occur in more than 50 % of all patients treated with conventional doses of azathioprine.

The frequency of undesirable effects has been classified as following:
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).

Infections 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.

Very rare: Cases of PML caused by the JC virus have been reported after using azathioprine in combination with other immunosuppressants (see section 4.4).

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 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 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: Depression of bone marrow function; leucopenia

Common: Thrombocytopenia

Uncommon: Anaemia

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

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

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.

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, 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 azathioprine should be carefully considered on an individual basis.

Respiratory, thoracic and mediastinal disorders

Very rare: Reversible pneumonitis

Gastrointestinal disorders

Very Common: Nausea and anorexia with occasional vomiting

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.

Pancreatitis has been reported in a small percentage of patients on azathioprine therapy, 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 degeneration of liver function tests

Rare: Life-threatening hepatic damage

Formatiert: Englisch (Großbritannien)

Formatiert: Englisch (Großbritannien)

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 / Hypersensitivity reactions).
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. If veno-occlusive disease is clinically suspected, azathioprine should be permanently withdrawn. 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

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of 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 [to be completed nationally].

4.9 Overdose

Symptoms and signs

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdose 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, though azathioprine is partially dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressive agents,
ATC code: L04AX01

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 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

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Determination of plasma concentrations of azathioprine or 6-MP have no prognostic values as regards effectiveness or toxicity of these compounds.

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:

a) The action of the released 6-MP as a purine antimetabolite.
b) The possible blockage of -SH groups by alkylation.
c) The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of immunocompetent cells (B- and T-lymphocytes).
d) 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 through 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 mercaptopurineribonucleotide, 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 faeces. There is no evidence of enterohepatic circulation.

Special Patient Populations
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, an active metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

5.3 Preclinical safety data

Teratogenicity or embryo lethality has been seen in a number of animal species with a varying degree of susceptibility. In rabbits, a dose of 5-15 mg/kg body weight daily on days 6-14 of pregnancy produced skeletal abnormalities; in mice and rats, doses of 1-2 mg/kg body weight daily on days 3-12 were lethal to the embryos.

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

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

Core:
Lactose Monohydrate
Microcrystalline Cellulose
Sodium Starch Glycollate (Type A) (Ph.Eur.)
Pregelatinised starch (maize)
Polysorbate 80
Povidone K30
Magnesium Stearate (Ph.Eur.) [plant]

Coating:
Opadry YS-1R-7006 Clear:

Hypromellose
Macrogol 400
Macrogol 6000

6.2 Incompatibilities

None known.

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

The film-coated tablets are packed in blister (clear-colourless PVC-PVdC film and hard tamper aluminium foil with VMCH heat sealing lacquer) in a carton box.

Pack sizes: 28, 30, 50, 56, 90 and 100 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Provided that the film-coating is intact, there is no risk in handling film-coated azathioprine tablets and no additional precautions are required. Do not crush the tablets. However, Azathioprine AqVida 50 mg should be handled in strict accordance with guidance for handling cytotoxic agents when the film-coated tablets were damaged.

Formatiert: Englisch (Großbritannien)
Formatiert: Englisch (Großbritannien)

Surplus medical products as well as contaminated appliances should be temporarily stored in clearly labeled containers and then discarded safely. High-temperature incineration is recommended.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

~~06/2016~~03/2017

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