Public Assessment Report
Decentralised Procedure

AZAFALK 75MG AND 100MG FILM-COATED TABLETS

(AZATHIOPRINE)

UK/H/2846/002-3/DC
UK Licence No: PL 08637/0023-4

DR FALK PHARMA GMBH
LAY SUMMARY

On 2nd December 2011, the UK granted Dr Falk Pharma GmbH Marketing Authorisations (licences) for Azafalk 75mg and 100mg film-coated tablets.

Azafalk 75mg and 100mg film-coated tablets contain the active ingredient azathioprine, which belongs to a group of medicines called immunosuppressives.

Immunosuppressives reduce the strength of your immune system.

Azafalk 75mg and 100mg film-coated tablets are used to:
- Help your body accept an organ transplant.
- Control some diseases where your immune system is reacting against your own body.

Azafalk 75mg and 100mg film-coated tablets can also be used alone or in combination with other medicines to treat:
- Severe rheumatoid arthritis.
- Severe inflammation of the gut (Crohn’s disease or ulcerative colitis).

Or to treat:
- Some diseases where your immune system is reacting against your own body (auto-immune diseases) including severe inflammatory diseases of the skin, liver, artery and some blood disorders.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Azafalk 75mg and 100mg film-coated tablets outweigh the risks and Marketing Authorisations have been granted.
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# Module 1

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| **MA Holder** | Dr. Falk Pharma GmbH  
Leinenweberstr. 5  
79108 Freiburg  
Germany |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Austria (AT), Belgium (BE), Germany (DE), Spain (ES), Hungary (HU), Lithuania (LT), Luxembourg (LU), the Netherlands (NL), Poland (PL), Portugal (PT), Slovenia (SI) and the Slovak Republic (SK). |
| **Procedure Number** | UK/H/2846/002-3/DC |
| **End of Procedure** | Day 210 – 19th October 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Azafalk 75mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 75mg azathioprine.
This product contains 87mg lactose per Azafalk 75mg film-coated tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Yellow round film-coated tablet, biconvex

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Azafalk is indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression).
Azafalk 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.
Azafalk is used as an immunopressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and/or 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.
Azafalk 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 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
For oral use.
The tablets should be taken with at least a glass of liquid (200ml).
The tablets should be taken during meals in order to decrease the risk of nausea.

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 1-4mg/kg/body weight/day and must be adjusted according to the clinical requirements and haematological tolerance.
Evidence indicates that Azafalk 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 1-3mg/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.
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.

For the treatment of auto-immune chronic active hepatitis the dosage is usually between 1.0 and 1.5mg/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. Azafalk is contra-indicated in severe hepatic impairment. (See section 4.3).

**Use in children and adolescents:**
There are insufficient data to recommend the use of Azafalk 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 Azafalk. 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 4.5).

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.

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

Crushing of the tablets should be avoided. If the film-coating of a tablet is damaged or the tablet is completely crushed, avoid skin contamination and inhalation of tablet particles (see sections 4.4 and 6.6).

For appropriate long-term dosing, other medicinal products containing 25mg should be used, if necessary.

### 4.3 Contraindications
- Hypersensitivity to the active substance azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients
- Severe infections
- Seriously impaired hepatic or bone marrow function
- Pancreatitis
- Any live vaccine, especially BCG, smallpox, yellow fever
- Pregnancy unless the benefits outweigh the risks (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 Azafalk 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 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).
• Limited data indicate that Azafalk is not effective in patients with hereditary hypoxanthineguanine-phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome). Therefore Azafalk should not be used in these patients.
• Coagulation should be closely monitored when anticoagulants of the coumarin type are given concomitantly with Azafalk (see section 4.5).
• Withdrawal of Azafalk can 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 Azafalk should always be a gradual process performed under close monitoring.
• If inactivated or toxoid vaccines are applied together with Azafalk, 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 Azafalk under supervision.

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 are at an increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas.

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).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

a) 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 section 4.2).

b) 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. Patients should be advised to inform their anaesthesiologist of their treatment with Azafalk prior to surgery.

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

d) 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.

e) 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).

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

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

h) 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).

i) 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.

j) 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).

k) 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 Pregnancy and lactation

Pregnancy
Azafalk 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.

**Effects on fertility**
Relief of chronic renal insufficiency by renal transplantation involving the administration of Azafalk has been accompanied by increased fertility in both male and female transplant recipients (for contraceptive measures see above).

**Lactation**
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).

**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.

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)

**Infection and infestations**
Transplant patients receiving azathioprine in combination with other immunosuppressants.
- Very common: Viral, fungal and bacterial infections.

Other indications.
- Uncommon: Viral, fungal and bacterial infections.

Patients receiving azathioprine alone, or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections.

**Neoplasms benign and malignant (including cysts and polyps)**
Rare: Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia (see also section 4.4).

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas, (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, is increased in patients who receive immunosuppressive drugs, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself. There have been rare reports of acute myeloid leukaemia and myelodysplasia (some in association with chromosomal abnormalities).
**Blood and lymphatic system disorders**

- **Very common:** Depression of bone marrow function; leucopenia.
- **Common:** Thrombocytopenia.
- **Uncommon:** Anaemia.
- **Rare:** Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.

Azathioprine may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leucopenia, but also sometimes as anaemia and thrombocytopenia, and rarely as agranulocytosis, pancytopenia and aplastic anaemia. These occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy. Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are 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, rechallenge 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 during meals (see section 4.2). 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

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 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.

4.9 Overdose

**Symptoms and signs**
Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with azathioprine and result from bone marrow depression which may be maximal after 9 to 14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5g 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 immunosuppressants;
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 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 methyl nitroimidazole 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:

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 thioanalogues.

5.2 Pharmacokinetic properties

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

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.

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 5-15mg/kg body weight daily on days 6-14 of pregnancy produced skeletal abnormalities. In mice and rats, doses of 1-2mg/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:
Croscarmellose sodium
Colloidal anhydrous silica
Lactose monohydrate
Microcrystalline cellulose
Sodium stearyl fumarate
Starch, pregelatinized
Povidone K25

Tablet coat:
Macrogol 3350
Polysorbate 80
Poly(vinyl alcohol)
Talc

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
The film-coated tablets are packed in PVC/aluminium blisters in a carton box.
The pack contains 20, 30, 50, 60, 90 or 100 film-coated 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, Azafalk film-coated tablets should be handled in strict accordance with guidance for handling cytotoxic agents when people have crushed the film-coated 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 product or waste material should be disposed of in accordance with local requirements.
In case of any visible signs of deterioration Azafalk film-coated tablets must not be used.

7 MARKETING AUTHORISATION HOLDER
Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 08637/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2011

10 DATE OF REVISION OF THE TEXT
02/12/2011
**NAME OF THE MEDICINAL PRODUCT**
Azafalk 100mg film-coated tablets

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 100mg azathioprine.
This product contains 116mg lactose per Azafalk 100mg film-coated tablet.

For a full list of excipients, see section 6.1.

**PHARMACEUTICAL FORM**
Film-coated tablet

Yellow round film-coated tablet, biconvex

**CLINICAL PARTICULARS**

4.1 Therapeutic indications
Azafalk is indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression).

Azafalk 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.

Azafalk is used as an immunopressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and/or 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.

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

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 1-4mg/kg/body weight/day and must be adjusted according to the clinical requirements and haematological tolerance.

Evidence indicates that Azafalk 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 1-3mg/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.

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.

For the treatment of auto-immune chronic active hepatitis the dosage is usually between 1.0 and 1.5mg/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. Azafalk is contra-indicated in severe hepatic impairment. (See section 4.3).

**Use in children and adolescents:**
There are insufficient data to recommend the use of Azafalk 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 Azafalk. 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 4.5).

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.

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

Crushing of the tablets should be avoided. If the film-coating of a tablet is damaged or the tablet is completely crushed, avoid skin contamination and inhalation of tablet particles (see sections 4.4 and 6.6).

For appropriate long-term dosing, other medicinal products containing 25mg should be used, if necessary.

### 4.3 Contraindications
- Hypersensitivity to the active substance azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients
- Severe infections
- Seriously impaired hepatic or bone marrow function
- Pancreatitis
- Any live vaccine, especially BCG, smallpox, yellow fever
- Pregnancy unless the benefits outweigh the risks (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 Azafalk 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 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).
- Limited data indicate that Azafalk is not effective in patients with hereditary hypoxanthineguanine-phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome). Therefore Azafalk should not be used in these patients.
- Coagulation should be closely monitored when anticoagulants of the coumarin type are given concomitantly with Azafalk (see section 4.5).
- Withdrawal of Azafalk can 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 Azafalk should always be a gradual process performed under close monitoring.
- If inactivated or toxoid vaccines are applied together with Azafalk, 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 Azafalk under supervision.

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 are at an increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas.

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).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

a) 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 section 4.2).

b) 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. Patients should be advised to inform their anaesthesiologist of their treatment with Azafalk prior to surgery.

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

d) 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.

e) 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).

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

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

h) 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).

i) 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.

j) 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).

k) 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 Pregnancy and lactation

Pregnancy

Azafalk 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.

**Effects on fertility**
Relief of chronic renal insufficiency by renal transplantation involving the administration of Azafalk has been accompanied by increased fertility in both male and female transplant recipients (for contraceptive measures see above).

**Lactation**
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).

### 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.

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)

**Infection and infestations**
Transplant patients receiving azathioprine in combination with other immunosuppressants.
- Very common: Viral, fungal and bacterial infections.

Other indications.
- Uncommon: Viral, fungal and bacterial infections.

Patients receiving azathioprine alone, or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections.

**Neoplasms benign and malignant (including cysts and polyps)**
Rare: Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia (see also section 4.4).

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas, (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, is increased in patients who receive immunosuppressive drugs, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself. There have been rare reports of acute myeloid leukaemia and myelodysplasia (some in association with chromosomal abnormalities).
Blood and lymphatic system disorders
Very common: Depression of bone marrow function; leucopenia.
Common: Thrombocytopenia.
Uncommon: Anaemia.
Rare: Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.

Azathioprine may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leucopenia, but also sometimes as anaemia and thrombocytopenia, and rarely as agranulocytosis, pancytopenia and aplastic anaemia. These occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy. Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are 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 during meals (see section 4.2). 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

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 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.

4.9 Overdose

**Symptoms and signs**

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with azathioprine and result from bone marrow depression which may be maximal after 9 to 14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5g 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 immunosuppressants;

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, thiоinosinic acid. The rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids. Irrespective of whether it is given directly or is derived in vivo from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methyl nitroimidazole 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:

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 thioanalogues.

5.2 Pharmacokinetic properties

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

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.

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 5-15mg/kg body weight daily on days 6-14 of pregnancy produced skeletal abnormalities. In mice and rats, doses of 1-2mg/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:
- Croscarmellose sodium
- Colloidal anhydrous silica
- Lactose monohydrate
- Microcrystalline cellulose
- Sodium stearyl fumarate
- Starch, pregelatinized
- Povidone K25

Tablet coat:
- Macrogol 3350
- Polysorbate 80
- Poly(vinyl alcohol)
- Talc

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
The film-coated tablets are packed in PVC/aluminium blisters in a carton box.
The pack contains 20, 30, 50, 60, 90 or 100 film-coated 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, Azafalk film-coated tablets should be handled in strict accordance with guidance for handling cytotoxic agents when people have crushed the film-coated 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 product or waste material should be disposed of in accordance with local requirements.
In case of any visible signs of deterioration Azafalk film-coated tablets must not be used.

7 MARKETING AUTHORISATION HOLDER
Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 08637/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2011

10 DATE OF REVISION OF THE TEXT
02/12/2011
Package Leaflet: Information for the User

Azafalk® 75mg film-coated tablets
Azathioprine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Azafalk 75mg tablets are and what they are used for
2. Before you take Azafalk 75mg tablets
3. How to take Azafalk 75mg tablets
4. Possible side effects
5. How to store Azafalk 75mg tablets
6. Further information

1. WHAT AZAFALK 75mg TABLETS ARE AND WHAT THEY ARE USED FOR

Azafalk 75mg tablets contain the active ingredient azathioprine, which belongs to a group of medicines called immunosuppressives.

Immunosuppressives reduce the strength of your immune system. Your doctor has prescribed Azafalk 75mg tablets for one of the following conditions:
- To help your body accept an organ transplant.
- To control some diseases where your immune system is reacting against your own body.

Azafalk 75mg tablets can also be used alone or in combination with other medicines to treat:
- severe rheumatoid arthritis
- severe inflammation of the gut (Crohn’s disease or ulcerative colitis)
or to treat:
- some diseases where your immune system is reacting against your own body (auto-immune diseases) including severe inflammatory diseases of the skin, liver, artery and some blood disorders.

2. BEFORE YOU TAKE AZAFALK 75mg TABLETS

Do not take Azafalk 75mg tablets if you:
- are allergic (hypersensitive) to azathioprine, mercaptopurine, or any of the ingredients of Azafalk 75mg tablets (see list of ingredients in Section 6). An allergic reaction may include rash, itching, difficulty of breathing or swelling of the face, lips, throat or tongue.
- have a severe infection
- have a severe liver or bone marrow disorder
- have pancreatitis (inflammation of the pancreas)
- have recently had a vaccination with a live vaccine such as smallpox or yellow fever
– are pregnant (unless your doctor tells you)
– are breast-feeding

**Take special care with Azafalk 75mg tablets**
You will not be given Azafalk 75mg tablets unless you can be monitored for side effects.
You should tell your doctor straight away if you develop ulcers of the throat, fever, infections, bruising, or bleeding.
Please consult your doctor
– if you are going to have a vaccination while you are taking Azafalk 75mg tablets
– if you have a condition where your body produces too little of a natural chemical called thiopurine methyltransferase (TPMT)
– if you suffer from a condition known as Lesch-Nyhan syndrome.

Patients taking immunosuppressive drugs may be more at risk of cancer, especially non-Hodgkin’s lymphoma, sarcoma (e.g. Kaposi’s and non-Kaposi’s), local cancer in the uterus and skin cancer. You should avoid strong sunlight or UV rays during the treatment with Azafalk 75mg tablets.

**Blood tests**
You will need a blood test once a week during the first 8 weeks of treatment. You may need blood tests more often if you:
– are elderly
– are taking a high dose
– have a liver or kidney disorder
– have a bone marrow disorder
– have an overactive spleen

It is important that you use effective contraception (such as condoms) as Azafalk 75mg tablets may cause birth defects when taken by either the man or woman.

**Warning:**
Any withdrawal of Azafalk 75mg tablets should be performed under close monitoring. Please ask your doctor.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, e.g.:
– **Allopurinol, oxipurinol or thiopurinol** (treatments for gout)
– **Muscle relaxants** such as curare, d-tubocurarine, pancuronium, or succinylcholine
– **Other immunosuppressants** such as cyclosporin or tacrolimus
– **Infliximab** (a treatment for Crohn’s disease)
– **Olsalazine, mesalazine or sulfasalazine** (treatments for ulcerative colitis)
– **Warfarin or phenprocoumon** (blood thinners)
– **ACE-inhibitors** (treatments for high blood pressure or heart failure)
– **Trimethoprim and sulphamethoxazole** (antibiotics)
– **Cimetidine** (a treatment for ulcers of the digestive tract)
– **Cancer treatments** or treatments that slow or stop the production of new blood cells
– **Furosemide** (a water tablet for heart failure)
– **Vaccines** such as hepatitis B
– **any “live” vaccine**
PAR Azafalk 75mg and 100mg film-coated tablets

Pregnancy and breast-feeding
You must not take Azafalk 75mg tablets if you are pregnant unless your doctor tells you to. Tell your doctor if you are or believe you might be pregnant. Both male and female patients of reproductive age should use a contraceptive other than an interuterine device (e.g. coil, Copper T). You should continue to use a contraceptive for three months after treatment with Azafalk 75mg tablets has stopped.

You must not breast-feed during treatment with Azafalk 75mg, as metabolic products produced in the body pass into the breast milk and can damage your child.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You are safe to drive or operate machinery when taking Azafalk 75mg tablets unless you experience dizziness. Dizziness maybe made worse by alcohol and you should not drive or operate machinery if you have been drinking alcohol.

Important information about some of the ingredients of Azafalk 75mg tablets
Azafalk 75mg tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE AZAFALK 75mg TABLETS

The tablets should be taken during meals with a glass of liquid.

Dosage
Patients who have had a transplant:
The usual first day dose is up to 5 mg/kg of body weight per day. The usual dose is then 1-4 mg/kg of body weight per day.

Other conditions:
The usual dosage is 1-3 mg/kg of body weight per day.

Children and adolescents:
Azafalk 75mg is not recommended for use in children below 18 years due to insufficient data for the treatment of juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis and polyarteritis nodosa.

For all other indications, the given dose recommendations apply for children and adolescents as well as for adults.

Elderly:
The elderly may need a reduced dose.

Patients with a liver or kidney disorder may need a reduced dose. Patients with severe liver disorder must not take Azafalk 75mg tablets.

The duration of treatment with Azafalk 75mg is determined by your doctor. Please ask your doctor if you think that the effect of Azafalk 75mg is too strong or too weak.
If you take more Azafalk 75mg tablets than you should:
Contact your doctor, pharmacist or nearest hospital immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Azafalk 75mg tablets can cause side effects, although not everybody gets them.

Adverse events are listed below by frequency.
Frequencies are defined as follows:
Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data

Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Serious side effects

If you develop any of the following side effects, contact your doctor immediately:
- Severe sickness
- Diarrhoea
- Fever, chills
- Muscle or bone pain, muscle stiffness
- Tiredness, dizziness
- Inflammation of the blood vessels
- Kidney disorders (symptoms may include changes in the amount of urine passed and changes in its colour)

The following side effects have also been reported:
**Very common:**
- infections in kidney transplant patients
- changes in the number of blood cells and platelets (these can be detected by a test carried out by a doctor)
- nausea (feeling sick)
- vomiting

**Common:**
- risk of infection in patients with bowel disease
- cancer
- inflammation of the pancreas
- liver disorders (these can be detected by a test carried out by a doctor)

**Uncommon:**
- infection in patients with rheumatoid arthritis
- raised liver enzymes or liver damage (these can be detected by a test carried out by a doctor)
- fatty pale stools
- hair loss

**Rare:**
- chest infection
- inflammation
- ulcers
- bleeding or damage in the digestive tract in patients having a transplant
- serious liver disease (this can be detected by a test carried out by a doctor)

**Very rare:**
- life-threatening allergic reactions.
If any of the side effects gets serious or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE AZAFALK 75mg TABLETS

Keep out of the reach and sight of children. Store in the original package to protect from light.

Do not use Azafalk 75mg tablets after the expiry date which is stated on the carton and blister after “EXP”. The expiry date refers to the last day of that month.

Do not use Azafalk 75 mg tablets if you notice any visible signs of deterioration.

Medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Azafalk 75mg tablets contain:
The active substance is azathioprine.
Each Azafalk 75mg film-coated tablet contains 75 mg azathioprine.

The other ingredients are:
Tablet core: croscarmellose sodium, colloidal anhydrous silica, lactose monohydrate, micro-crystalline cellulose, sodium stearyl fumarate, starch pregelatinized, povidone K25
Tablet coat: Macrogol 3350, Polysorbate 80, Poly(vinyl alcohol), Talc

What Azafalk 75mg tablets look like and contents of the pack
Azafalk 75mg film-coated tablets are yellow, round, biconvex tablets marked “75” on one side.

Crushing of the tablets should be avoided. If the film-coating of a tablet is damaged or the tablet is completely crushed, avoid skin contamination and inhalation of tablet particles. For appropriate long-term dosing other medicinal products containing 25 mg should be used, if necessary.

Packaging:
The film-coated tablets are packed in PVC/aluminium blisters in a carton box.
Azafalk 75mg tablets are available in packs of: 20, 30, 50, 60, 90 or 100 film-coated tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
DR. FALK PHARMA GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

Tel.: +49 (0) 761/1514-0
Fax: +49 (0) 761/1514-321
E-Mail: zentrale@drfalkpharma.de

This medicinal product is authorised in the Member States of the EEA under the following names:
Austria, Belgium, Germany, Great Britain, Hungary, Latvia, Luxembourg, The Netherlands, Poland, Portugal, Slovakia and Slovenia: Azafalk®.
Spain: Immufalk®.

This leaflet was last approved in 10/2011.
The following information is intended for medical or healthcare professionals only:

AZAFALK 75mg film-coated Tablets

Instructions for use and handling and disposal
There are no risks associated with handling tablets with intact coating. In that case no special safety precautions are necessary. However, Azafalk film-coated tablets should be handled in strict accordance with guidance for handling cytotoxic agents when people have crushed the film-coated tablets. Surplus medical products as well as contaminated appliances should be temporarily stored in clearly labelled containers. Any unused product or waste material should be disposed of in accordance with local requirements.
Immunosuppressives reduce the strength of your immune system. Your doctor has prescribed Azafalk 100mg tablets for one of the following conditions:
- To help your body accept an organ transplant.
- To control some diseases where your immune system is reacting against your own body.

Azafalk 100mg tablets can also be used alone or in combination with other medicines to treat:
- severe rheumatoid arthritis
- severe inflammation of the gut (Crohn’s disease or ulcerative colitis)
or to treat:
- some diseases where your immune system is reacting against your own body (auto-immune diseases) including severe inflammatory diseases of the skin, liver, artery and some blood disorders.

2. BEFORE YOU TAKE AZAFALK 100mg TABLETS

Do not take Azafalk 100mg tablets if you:
- are allergic (hypersensitive) to azathioprine, mercaptopurine, or any of the ingredients of Azafalk 100mg tablets (see list of ingredients in Section 6). An allergic reaction may include rash, itching, difficulty of breathing or swelling of the face, lips, throat or tongue.
- have a severe infection
- have a severe liver or bone marrow disorder
- have pancreatitis (inflammation of the pancreas)
- have recently had a vaccination with a live vaccine such as smallpox or yellow fever
– are pregnant (unless your doctor tells you)
– are breast-feeding

**Take special care with Azafalk 100mg tablets**
You will not be given Azafalk 100mg tablets unless you can be monitored for side effects. You should tell your doctor straight away if you develop ulcers of the throat, fever, infections, bruising, or bleeding.

Please consult your doctor
– if you are going to have a vaccination while you are taking Azafalk 100mg tablets
– if you have a condition where your body produces too little of a natural chemical called thiopurine methyltransferase (TPMT)
– if you suffer from a condition known as Lesch-Nyhan syndrome.

Patients taking immunosuppressive drugs may be more at risk of cancer, especially non-Hodgkin’s lymphoma, sarcoma (e.g. Kaposi’s and non-Kaposi’s), local cancer in the uterus and skin cancer. You should avoid strong sunlight or UV rays during the treatment with Azafalk 100mg tablets.

**Blood tests**
You will need a blood test once a week during the first 8 weeks of treatment. You may need blood tests more often if you:
– are elderly
– are taking a high dose
– have a liver or kidney disorder
– have a bone marrow disorder
– have an overactive spleen

It is important that you use effective contraception (such as condoms) as Azafalk 100mg tablets may cause birth defects when taken by either the man or woman.

**Warning:**
Any withdrawal of Azafalk 100mg tablets should be performed under close monitoring. Please ask your doctor.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, e.g.:
– Allopurinol, oxipurinol or thiopurinol (treatments for gout)
– Muscle relaxants such as curare, d-tubocurarine, pancuronium, or succinylcholine
– Other immunosuppressants such as cyclosporin or tacrolimus
– Infliximab (a treatment for Crohn’s disease)
– Olsalazine, mesalazine or sulfasalazine (treatments for ulcerative colitis)
– Warfarin or phenprocoumon (blood thinners)
– ACE-inhibitors (treatments for high blood pressure or heart failure)
– Trimethoprim and sulphamethoxazole (antibiotics)
– Cimetidine (a treatment for ulcers of the digestive tract)
– Cancer treatments or treatments that slow or stop the production of new blood cells
– Furosemide (a water tablet for heart failure)
– Vaccines such as hepatitis B
– any “live” vaccine
Pregnancy and breast-feeding
You must not take Azafalk 100mg tablets if you are pregnant unless your doctor tells you to.
Tell your doctor if you are or believe you might be pregnant. Both male and female patients of reproductive age should use a contraceptive other than an intrauterine device (e.g. coil, Copper T). You should continue to use a contraceptive for three months after treatment with Azafalk 100mg tablets has stopped.
You must not breast-feed during treatment with Azafalk 100mg, as metabolic products produced in the body pass into the breast milk and can damage your child.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You are safe to drive or operate machinery when taking Azafalk 100mg tablets unless you experience dizziness. Dizziness may be made worse by alcohol and you should not drive or operate machinery if you have been drinking alcohol.

Important information about some of the ingredients of Azafalk 100mg tablets
Azafalk 100mg tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE AZAFALK 100mg TABLETS
The tablets should be taken during meals with a glass of liquid.

Dosage
Patients who have had a transplant:
The usual first day dose is up to 5 mg/kg of body weight per day. The usual dose is then 1-4 mg/kg of body weight per day.

Other conditions:
The usual dosage is 1-3 mg/kg of body weight per day.

Children and adolescents:
Azafalk 100mg is not recommended for use in children below 18 years due to insufficient data for the treatment of juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis and polyarteritis nodosa.
For all other indications, the given dose recommendations apply for children and adolescents as well as for adults.

Elderly:
The elderly may need a reduced dose.

Patients with a liver or kidney disorder may need a reduced dose. Patients with severe liver disorder must not take Azafalk 100mg tablets.
The duration of treatment with Azafalk 100mg is determined by your doctor. Please ask your doctor if you think that the effect of Azafalk 100mg is too strong or too weak.
If you take more Azafalk 100mg tablets than you should:
Contact your doctor, pharmacist or nearest hospital immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Azafalk 100mg tablets can cause side effects, although not everybody gets them.

Adverse events are listed below by frequency. Frequencies are defined as follows:
Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data

Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Serious side effects

If you develop any of the following side effects, contact your doctor immediately:
- Severe sickness
- Diarrhoea
- Fever, chills
- Muscle or bone pain, muscle stiffness
- Tiredness, dizziness
- Inflammation of the blood vessels
- Kidney disorders (symptoms may include changes in the amount of urine passed and changes in its colour)

The following side effects have also been reported:
Very common:
- Infections in kidney transplant patients
- Changes in the number of blood cells and platelets (these can be detected by a test carried out by a doctor)
- Nausea (feeling sick)
- Vomiting

Common:
- Risk of infection in patients with bowel disease
- Cancer
- Inflammation of the pancreas
- Liver disorders (these can be detected by a test carried out by a doctor)

Uncommon:
- Infection in patients with rheumatoid arthritis
- Raised liver enzymes or liver damage (these can be detected by a test carried out by a doctor)
- Fatty pale stools
- Hair loss

Rare:
- Chest infection
- Inflammation
- Ulcers
- Bleeding or damage in the digestive tract in patients having a transplant
- Serious liver disease (this can be detected by a test carried out by a doctor)

Very rare:
- Life-threatening allergic reactions.
If any of the side effects gets serious or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE AZAFALK 100mg TABLETS

Keep out of the reach and sight of children. Store in the original package to protect from light.

Do not use Azafalk 100mg tablets after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

Do not use Azafalk 100 mg tablets if you notice any visible signs of deterioration.

Medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Azafalk 100mg tablets contain:

The active substance is azathioprine. Each Azafalk 100mg film-coated tablet contains 100 mg azathioprine.

The other ingredients are:
Tablet core: croscarmellose sodium, colloidal anhydrous silica, lactose monohydrate, micro-crystalline cellulose, sodium stearyl fumarate, starch pregelatinized, povidone K25
Tablet coat: Macrogol 3350, Polysorbate 80, Poly(vinyl alcohol), Talc

What Azafalk 100mg tablets look like and contents of the pack
Azafalk 100mg film-coated tablets are yellow, round, biconvex tablets marked "100" on one side.

Crushing of the tablets should be avoided. If the film-coating of a tablet is damaged or the tablet is completely crushed, avoid skin contamination and inhalation of tablet particles. For appropriate long-term dosing other medicinal products containing 25 mg should be used, if necessary.

Packaging:
The film-coated tablets are packed in PVC/aluminium blisters in a carton box.
Azafalk 100mg tablets are available in packs of: 20, 30, 50, 60, 90 or 100 film-coated tablets
Not all packs sizes may be marketed.

Marketing Authorisation Holder:
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79108 Freiburg
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AZAFALK 100mg film-coated Tablets

Instructions for use and handling and disposal
There are no risks associated with handling tablets with intact coating. In that case no special safety precautions are necessary. However, Azafalk film-coated tablets should be handled in strict accordance with guidance for handling cytotoxic agents when people have crushed the film-coated tablets. Surplus medical products as well as contaminated appliances should be temporarily stored in clearly labelled containers. Any unused product or waste material should be disposed of in accordance with local requirements.
Module 4
Labelling

Please note that the labelling shown below is for the 50 film-coated tablet pack size only. The marketing authorisation holder has stated that it does not intend to market the 20, 30, 60, 90 and 100 film-coated tablet pack sizes and, thus, no UK-specific label mock-ups have been provided. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the 20, 30, 60, 90 and 100 film-coated tablet pack sizes.
Azafalk 75mg film-coated tablets

Azathioprine

50 film-coated tablets

Oral use
Each film-coated tablet contains 75 mg azathioprine.
Contains lactose monohydrate. See leaflet for further information.
Store in the original package in order to protect from light.
Read the package leaflet before use.
Keep out of the reach and sight of children.

[Barcode]
PL00037/0023
Module 5
Scientific discussion during initial procedure

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Austria (AT), Belgium (BE), Germany (DE), Spain (ES), Hungary (HU), Lithuania (LT), Luxembourg (LU), the Netherlands (NL), Poland (PL), Portugal (PT), Slovenia (SI), the Slovak Republic (SK) and the UK considered that the applications for Azafalk 75mg and 100mg film-coated tablets could be approved. These products are prescription only medicines (POM) and are indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression).

Azafalk 75mg and 100mg film-coated tablets are indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic kidney, liver, heart, lung, or pancreas transplants.

Azafalk 75mg and 100mg film-coated tablets are used as immunosuppressant antimetabolites either alone or, more commonly, in combination with other agents (usually corticosteroids) and/or procedures which influence the immune response.

Azafalk 75mg and 100mg film-coated tablets are 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 and polymyositis
- auto-immune chronic active hepatitis
- polyarteritis nodosa
- auto-immune haemolytic anaemia
- chronic refractory idiopathic thrombocytopenic purpura

These applications for Azafalk 75mg and 100mg film-coated tablets were submitted as abridged applications according to Article 10.3 of Directive 2001/83/EC, claiming to be hybrid medicinal products to Imuran 50mg tablets, authorised in the UK to Aspen Europe GmbH on 3rd October 1986 (PL 35468/0010).

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and a methylnitroimidazole moiety. Azathioprine has cytotoxic and immunosuppressive effects.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. With the exception of the bioequivalence study, no clinical studies have been performed and none are required for this application as the pharmacology of azathioprine is well-established.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan was provided. The MAH committed to perform studies and additional pharmacovigilance activities.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Azafalk 75mg and 100mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other immunosuppressants (L04AX01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>75mg and 100mg film-coated tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/2846/002-3/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Austria (AT), Belgium (BE), Germany (DE), Spain (ES), Hungary (HU), Lithuania (LT), Luxembourg (LU), the Netherlands (NL), Poland (PL), Portugal (PT), Slovenia (SI) and the Slovak Republic (SK)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 08637/0023-4</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Dr. Falk Pharma GmbH Leinenweberstr. 5 79108 Freiburg Germany</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

Paracetamol
INN/Ph.Eur name:  Azathioprine
Chemical name:  6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)thio]-1H-purine
                6-((1-Methyl-4-nitroimidazol-5-yl)thio)-purine
                6-(Methyl-p-nitro-5-imidazolyl)-thiopurine

Structural formula:

\[ \text{Structural formula image} \]

Molecular formula:  \( \text{C}_9\text{H}_7\text{N}_7\text{O}_2\text{S} \)
Molecular weight:  277.26

Appearance:  Pale yellow crystalline powder.
Solubility:  Insoluble in water and very slightly soluble in ethanol.

Azathioprine is the subject of a European Pharmacopoeia monograph.

Azathioprine is the subject of a Certificate of Suitability; therefore all aspects of the manufacture of the active substance from its starting materials have been assessed and found satisfactory.

All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods are in line with the European Pharmacopoeia monograph and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. The reference standards used are in line with the European Pharmacopoeia monograph.

The container-closure system and retest period are satisfactory and comply with the details given on the EDQM Certificate of Suitability.

P.  Medicinal Product

Other Ingredients

Other ingredients in the tablet core are pharmaceutical excipients croscarmellose sodium, colloidal anhydrous silica, lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, pregelatinized starch and povidone K25.

The excipient in the tablet coating is Opadry II 85F19250 clear (macrogol 3350, polysorbate 80, poly(vinyl alcohol) and talc).
With the exception of Opadry II 85F19250 clear, all excipients comply with their respective European Pharmacopoeia monographs. Opadry II 85F19250 clear complies with in-house specifications. The components of Opadry II 85F19250 clear all comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to produce azathioprine containing products that could be considered equivalent hybrid medicinal products of Imuran 50mg tablets.

The applicant has provided suitable product development information. Valid justification for the use and amount of each excipient has been provided.

Satisfactory comparative *in vitro* dissolution profiles and impurity profiles have been provided for the finished product versus the reference product.

The reference product used in the bioequivalence study is Imurek 50mg tablets, licensed in Germany to GlaxoSmithKline GmbH. This product is considered to be pharmaceutically equivalent to the UK reference product.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on batches have been provided. The applicant has committed to perform process validation on full commercial-scale batches post approval.

**Finished Product Specification**

The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

The products are packaged in blisters composed of polyvinyl chloride and aluminium, further packaged in a carton box. Pack sizes for both strengths are 20, 30, 50, 60, 90 and 100 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with relevant EU legislation.
Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a satisfactory shelf-life of 3 years with the storage instructions ‘Store in the original package in order to protect from light’.

Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labelling
The SmPCs, PILs and labelling are pharmaceutically acceptable.

A satisfactory bridging report to the user testing of Azathioprine 50mg film-coated tablets (PL 32019/0022) which was approved to Roger Oakes Limited on 28th November 2008 has been provided. Regarding the lay-out and structure of the PIL a satisfactory bridging report for an already approved PIL for Salofalk 1000mg gastro-resistant prolonged release granules, authorised to Dr Falk Pharma GmbH on 1st September 2003 (PL 08637/0008) was provided. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA (Marketing Authorisation Application) forms
The MAA forms are pharmaceutically satisfactory.

Overall Summary
The pharmaceutical overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of azathioprine are well-known. As azathioprine is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required. An overview based on literature is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

A single-dose, randomised, two-period, two-sequence, crossover open-label study to compare the pharmacokinetics of the test product Azafalk 100mg film-coated tablets versus the reference product Imurek (2x) 50mg Tablets (GlaxoSmithKline GmbH) in healthy subjects under fed conditions.

Blood samples were taken pre- and up to 24 hours post dose. There was a washout period of at least 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed. The active metabolite for azathioprine, 6-mercaptopurine is also responsible for the effect of the medicinal product, therefore this was also measured.

Results for azathioprine and 6-mercaptopurine are presented below as log-transformed values for geometric means:

### Azathioprine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(0-τ) (h*ng/mL)</th>
<th>AUC(0-∞) (h*ng/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>27.04</td>
<td>32.15</td>
<td>21.45</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>27.81</td>
<td>32.33</td>
<td>20.63</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>97.2 (93.3 – 101.4)</td>
<td>99.5 (93.7 – 105.6)</td>
<td>104.0 (92.5 – 116.9)</td>
</tr>
</tbody>
</table>

- AUC(0-τ): area under the plasma concentration-time curve from time zero to t hours
- AUC(0-∞): area under the plasma concentration-time curve from time zero to infinity
- C_{max}: maximum plasma concentration

### 6-mercaptopurine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(0-τ) (h*ng/mL)</th>
<th>AUC(0-∞) (h*ng/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>50.21</td>
<td>55.37</td>
<td>23.85</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>51.67</td>
<td>55.90</td>
<td>24.47</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>97.2 (87.8 – 107.6)</td>
<td>99.1 (88.8 – 110.5)</td>
<td>97.5 (82.6 – 115.1)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90 % confidence intervals for test/reference ratios of geometric means for AUC_{0-τ} and C_{max} for azathioprine and its metabolite, 6-mercaptopurine lie within acceptable limits (80.00-125.00 %). Thus, bioequivalence has been shown between the test and reference products in this study.

As the 75 mg product met all the criteria that are specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) for a
biowaiver for the lower strength, the results and conclusions of the bioequivalence study with the 100mg strength can be extrapolated to Azafalk 75mg film-coated tablets.

**Efficacy**
With the exception of the data submitted relating to the bioequivalence study, no new efficacy data were submitted with these generic applications and none were required.

**Safety**
With the exception of the data submitted relating to the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling**
The SmPCs, PILs and labelling are clinically satisfactory and consistent with those for the reference products.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**MAA Forms**
The MAA forms are clinically satisfactory.

**Conclusions**
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Azafalk 75mg and 100mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
The applicant’s Azafalk 100mg film-coated tablets and the reference product Imuran (2x) 50mg tablets are considered to be bioequivalent. As the 75 mg product met the criteria for a biowaiver, Azafalk 75mg film-coated tablets are also considered to be bioequivalent to the reference product.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference product.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with azathioprine is considered to have demonstrated the therapeutic value of the compound. The risk benefit assessment is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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