TITLE
Azathioprine.

SCOPE

Trade name
IMURAN INJECTION ™

Formulation and Strength
Powder for solution for injection/infusion.
Each vial contains 50 mg of the active ingredient azathioprine as the sodium salt.

Excipients
Sodium hydroxide*
Water for injections(removed during processing).
Nitrogen Oxygen-Free

*The sodium ion content of the injection formulation is approximately 4.5 mg (0.2 mEq).

CLINICAL INFORMATION

Indications
Facilitates the survival and function of organ transplant

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

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

Dosage and Administration

GENERAL
Azathioprine injection should be used ONLY when the oral route is impractical, and should be discontinued as soon as oral therapy is tolerated. It must be administered only by the intravenous route. Specialist medical literature should be consulted for guidance as to clinical experience in particular conditions.

Administration
Azathioprine Injection, when reconstituted as directed, is a very irritant solution with a pH of 10–12. When the reconstituted solution is diluted as directed (see Use and Handling – Reconstitution and dilution of azathioprine injection), the pH of the resulting solution may be expected to be within the range pH 8.0 to 9.5 (the greater the dilution, the lower the pH).
Where dilution of Azathioprine injection is not practicable, the reconstituted solution should be injected slowly over a period of not less than one minute and followed immediately by not less than 50 ml of one of the recommended infusion solutions (see Use and Handling – Reconstitution and dilution of azathioprine injection).

Care must be taken to avoid perivenous injection which may produce tissue damage.

**Populations**

- **Adults**
  - **TRANSPLANTS**
    Depending on the immunosuppressive regimen employed, a dosage of up to 5 mg/kg bodyweight/day may be given on the first day of therapy, either orally or intravenously.

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

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

- **Children**
  - **TRANSPLANTS**
    See Dosage and Administration – Adults - Transplants.

- **Elderly (see Dosage and Administration - Renal impairment and Hepatic impairment):**
  There is a limited experience of the administration of azathioprine to elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with azathioprine, it is recommended that the dosage used should be at the lower end of the range. *(see Dosage and Administration – Adults).*

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

- **Renal impairment**
  In patients with renal insufficiency, dosages should be given at the lower end of the normal range (see Warnings and Precautions).

- **Hepatic impairment**
  In patients with hepatic insufficiency, dosages should be given at the lower end of the normal range *(see Warnings and Precautions).*

**Contraindications**

Azathioprine is contra-indicated in patients known to be hypersensitive to azathioprine or any other component of the preparation.

Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to azathioprine.

Azathioprine therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant in the near future *(see Warnings and Precautions).*
Warnings and precautions

Monitoring
There are potential hazards in the use of azathioprine. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used, or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

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

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 coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6–mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see Adverse Reactions). Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.

Renal and/or hepatic insufficiency:
It has been suggested that the toxicity of azathioprine may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion.

Nevertheless, it is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs.

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

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

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

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the offspring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with azathioprine.

Azathioprine and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders.
**Effects on fertility:**
Relief of chronic renal insufficiency by renal transplantation involving the administration of azathioprine has been accompanied by increased fertility in both male and female transplant recipients.

**Carcinogenicity:** (see Adverse Reactions)
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.

Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level. As is usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited, and patients should wear protective clothing and use a sunscreen with a high protection factor.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with IMURAN. These cases have had a very aggressive disease course and have been fatal. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Some of the patients were treated with IMURAN as monotherapy and some had received concomitant treatment with a TNFα blocker at or prior to diagnosis. The safety and efficacy of IMURAN for the treatment of Crohn's disease and ulcerative colitis have not been established.

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

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

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

**Interactions**

**Allopurinol/oxipurinol/thiopurinol:**
Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6-thioguanosine acid to biologically inactive 6-thioric acid. When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6-mercaptopurine or azathioprine, the dose of 6-mercaptopurine and azathioprine should be reduced to one-quarter of the original dose.

**Neuromuscular blocking agents:**
Azathioprine can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and can reduce the blockade produced by non-depolarising agents such as tubocurarine. There is considerable variation in the potency of this interaction.
Warfarin:
Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine, has been reported.

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

There has been a case report suggesting that haematological abnormalities may develop due to the concomitant administration of azathioprine and captopril.

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

Aminosalicylates
As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine therapy (see warnings and precautions).

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

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

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.

Pregnancy and lactation

Fertility
See Warnings and Precautions – Effects on fertility.

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

Evidence of the teratogenicity of azathioprine in man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving azathioprine.

There have been reports of premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure.
Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine.

Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy.

**Lactation**
6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

**Ability to perform tasks that require judgement, motor or cognitive skills**
There are no data on the effect of azathioprine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

**Adverse Reactions**
For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: very common: >1/10, common: ≥1/100, < 1/10, uncommon: ≥1/1000 and <1/100, rare: ≥1/10,000 and <1/1000, very rare: <1/10,000.

Infections and infestations
Very common: viral, fungal and bacterial infections in transplant patients receiving azathioprine in combination with other immunosuppressants.
Uncommon: viral, fungal and bacterial infections in other patient populations.

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

**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 Warnings and Precautions).

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).

Very rare: Hepatosplenic T-cell lymphoma in patients with IBD when used in combination with anti-TNF agents.

**Blood and lymphatic system disorders**
Very common: depression of bone marrow function; leucopenia.
Common: thrombocytopenia.
Uncommon: anaemia.
Rare: agranulocytosis, pancytopenia, aplastic anemia, 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 tablets and injection. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis (see *Adverse Reactions - 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 tablets and injection, the necessity for continued administration should be carefully considered on an individual basis.

**Respiratory, thoracic and mediastinal disorders**

Very rare: reversible pneumonitis.

**Gastrointestinal disorders**

Uncommon: pancreatitis.
Very rare: colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.

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 rechallenge, has been reported in patients treated with azathioprine for inflammatory bowel disease. The possibility that exacerbation of symptoms might be drug-related should be borne in mind when treating such patients.

Pancreatitis has been reported in a small percentage of patients 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 rechallenge has confirmed an association with azathioprine on occasions.
**Hepato-biliary disorders**

Uncommon: cholestasis and deterioration 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 Adverse Reactions - Immune system disorders).

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

**Skin and subcutaneous tissue disorders**

Rare: alopecia.

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.

**Overdosage**

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

**Treatment:**
There is no specific antidote. Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. The value of dialysis in patients who have taken an overdose of azathioprine is not known, though azathioprine is partially dialysable.

**Clinical Pharmacology**

**Pharmacodynamics**

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

The release of 6-MP which acts as a purine antimetabolite.

The possible blockade of -SH groups by alkylation.

The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.

Damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.
Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment.

**Pharmacodynamic Effects**

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP.

Plasma levels of azathioprine and 6-mercaptopurine do not correlate well with the therapeutic efficacy or toxicity of azathioprine, and therefore have no prognostic value.

**Pharmacokinetics**

**Distribution**

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

Nucleotides formed in the metabolism of azathioprine do not traverse cell membranes and therefore do not circulate in body fluids.

**Metabolism**

Azathioprine is rapidly broken down in vivo into 6-MP and a methyl nitroimidazole moiety. The 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Oxidation of 6-MP to the inactive metabolite, thiouric acid, is brought about by xanthine oxidase, an enzyme which is inhibited by allopurinol.

**Elimination**

6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid, irrespective of whether it is given directly or is derived in vivo from azathioprine.

**NON-CLINICAL INFORMATION**

**Reproductive toxicology**

Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5 to 15 mg/kg bodyweight/day over the period of organogenesis have shown varying degrees of foetal abnormalities.

Teratogenicity was evident in rabbits at 10 mg/kg bodyweight/day.

**PHARMACEUTICAL INFORMATION**

**Incompatibilities**

Azathioprine Injection should not be mixed with other drugs or fluids, except those specified in Use and Handling.

**Shelf life**

3 years unopened.
5 days when reconstituted with 5 ml to 15 ml water for injections and stored at 5°C to 25°C.
1 day for 5 ml of the reconstituted injection further diluted with between 20 ml and 200 ml of an appropriate infusion solution and stored at 15°C to 25°C.
Storage

Store below 25°C.
Keep dry. Protect from light.

Nature and contents of container

Neutral glass vials with synthetic butyl rubber closures and aluminium collars. Each vial contains the equivalent of 50 mg azathioprine.

Use and Handling

Safe handling

Health professionals who handle azathioprine Injection should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations.

Azathioprine Injection should be prepared for administration either by or under the direct supervision of a pharmacist, or by another specially trained person, who is familiar with its properties and has expertise in the safe handling of similar preparations.

Azathioprine Injection should be prepared for use in the aseptic unit of a pharmacy, which is equipped with a suitable vertical laminar flow cabinet designed to ensure adequate protection of both operator and product and, preferably, reserved solely for cytotoxic preparations. Where such a facility does not exist, a specially designated side room of a ward or clinic may be used.

Personnel involved with the preparation of azathioprine Injection should wear the following protective clothing:

- Polyvinylchloride disposable gloves of a suitable quality (rubber gloves are not adequate);
- Surgical face-mask of suitable quality;
- Protective goggles or glasses which should be washed thoroughly with water after use;
- Disposable apron. In an aseptic facility, other suitable clothing will be required.

Any spillage should be dealt with immediately, by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag after use. Contaminated surfaces should be washed with copious quantities of water.

Should azathioprine Injection solution come into contact with the skin, the skin should be washed thoroughly with soap and plenty of cold water.

If the eyes are contaminated, immediate irrigation with sodium chloride eye wash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of clean tap water may be used.

Reconstitution and dilution of azathioprine Injection:

Precautions should always be taken when handling azathioprine Injection (see Use and Handling - Safe handling).
No antimicrobial preservative is included. Therefore, reconstitution and dilution must be carried out under full aseptic conditions, preferably immediately before use. Any unused solution should be discarded. (see Disposal).
The contents of each vial should be reconstituted by the addition of 5 ml to 15 ml of Water for Injections BP. The reconstituted solution is stable for up to 5 days when stored between 5°C and 25°C. When diluted on the basis of 5 ml of reconstituted solution to a volume of between 20 ml and 200 ml of one of the following infusion solutions, azathioprine is stable for up to 24 hours at room temperature (15°C to 25°C):

- Sodium Chloride Intravenous Infusion BP (0.45% w/v and 0.9% w/v).
- Sodium Chloride (0.18% w/v)
- Glucose (4.0% w/v) Intravenous Infusion BP.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solution the preparation must be discarded.
Azathioprine Injection should ONLY be reconstituted with the recommended volume of Water for Injections BP and should be diluted as specified above.

When azathioprine injection is reconstituted as directed, it is a very irritant solution with a pH of 10 to 12. When the reconstituted solution is diluted as directed, the pH of the resulting solution may be expected to be within the range pH 8.0 to 9.5 (the greater the dilution, the lower the pH).

**Administration:**
The patient’s eyes, skin and mucous membranes should be protected from contact with the reconstituted or diluted solution; care should be taken, however, to ensure that the patient is not made unduly anxious by the procedures used.

The patient’s clothing, body and bedding should be protected by use of an absorbent disposable layer on top of a waterproof layer.

**Disposal:**
Azathioprine Injection solution should be disposed of in an appropriate manner (for example, deep burial or high-temperature incineration) according to local regulatory requirements.

Disposal of sharp objects, such as needles, syringes, administration sets and ampoules should be in rigid containers labeled with a suitable hazard warning seal. Personnel involved in disposal should be aware of the precautions to be observed, and the material should be destroyed in accordance with local regulatory requirements which may include incineration.

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123-71-20448

26.10.2011