SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexamed 4mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each milliliter of aqueous solution contains the equivalent of 4mg of dexamethasone phosphate as dexamethasone sodium phosphate (equivalent to about 3.33mg dexamethasone).

Excipient with known effect: benzyl alcohol. Each milliliter of aqueous solution contains 20.9mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

Injection is indicated for use in all forms of general and local glucocorticoid injection therapy and in acute cases in which oral glucocorticoid therapy is not feasible and intravenous glucocorticoid therapy maybe life-saving. For systemic administration by intravenous or intramuscular injection:
Allergy and anaphylaxis: Short term management of acute self-limited allergic conditions such as angioneurotic oedema or acute exacerbations of chronic allergic disorders such as bronchial asthma, including status asthmaticus, or serum sickness, post medication allergic reactions, post transfusion reactions, serum disease, oedema of larynx, anaphylactic reactions, contact dermatitis and other dermatitis, allergic rhinitis.
Gastro-intestinal tract: Crohn's disease, ulcerative colitis
Infection (with appropriate chemotherapy): military tuberculosis and endotoxic shock, impairment in serum disease in tbc, tbc meningitis.
Shock: Dexamed is used as adjunctive treatment of shock, of haemorrhagic, traumatic, surgical or septic origin. Treatment is an adjunct and therefore must be accompanied by comprehensive shock therapy

such as increasing of volume of circulating blood, adjustment of electrolyte balance, administration of oxygen, surgical intervention, contingent administration of antibiotics, infusion therapy with catecholamines.

Cerebral oedema: post traumatic or connected with an expansion process (raised intra-cranial pressure secondary to cerebral tumours and infantile spasms). Post-surgical preventive care even in patients with secondary elevated intracranial pressure. Also, in palliative care in case of non-operable cerebral tumours.

Other indications: aspiration pneumonia together with antibiotics, rheumatoid arthritis, collagenosis, nephritic syndrome, lymphatic leukaemia and other indications for oral treatment with glucocorticoids, where oral administration is not possible.

Local administration: it is suitable for intra-articular or soft tissue administration, as both short term and adjunctive therapy in:

Adjuvant short-term therapy in acute disease or acute exacerbation: rheumatoid arthritis, osteroarthritis with inflammation, carpal tunnel syndrome, synovitis, irritated arthritis, bursitis, gouty arthritis, epicondylitis, fibrositis, tendovaginitis.

It may be injected intralesionally in skin disorders such as cystic acne vulgaris, localized lichen simplex and keloids.

4.2. Posology and method of administration

NOTE: doses are expressed as mg dexamethasone phosphate. Dexamethasone phosphate 4mg is equivalent to approximately 3.33mg dexamethasone.

Glucocorticoid dosage generally depends on the patient response and the severity of the condition. In certain circumstances, such as a change in the clinical prognosis, or in stress, extra dosage adjustments may be needed. The lowest effective dose should be used for the minimum period and this should be reviewed frequently to appropriately titrate the dose against disease activity.

Adults

Dosage must be individualised to the patient and to the disease. The lowest possible dosage to control the disease must be used to minimise side effects. Usual parenteral dose range is one third to half the oral dose, given every twelve hours. Usual initial dose is 0.5mg to 20mg (0.125ml - 5ml) a day. Initial dosage should be maintained or adjusted until a satisfactory response is noted. When a favourable response is obtained, the effective maintenance dose should be determined by decrease of dose at suitable intervals and by small increments to obtain the lowest dose with satisfactory clinical response. Chronic dosage should not exceed the equivalent of 0.5mg dexamethasone per day (equivalent to 0.6mg dexamethasone phosphate, 0.15ml injection). If treatment is stopped following administration for more than a few days, it should be done gradually.

Shock (of surgical, traumatic or haemorrhagic origin): usually 2mg - 6mg/kg bodyweight as a single intravenous injection. It can be repeated in two to six hours if shock persists. High doses should only be administered until the patient's condition has stabilised, usually no longer than 48 - 72 hours.
This bolus injection can then be followed by continuous IV infusion of 3mg/kg bodyweight per 24 hours.

Cerebral oedema: associated with primary/metastatic brain tumour, pre-operative preparation of patients with increased intracranial pressure secondary to brain tumour, 10mg intravenously followed by 4mg intramuscularly every six hours until subsidence of symptoms. Response is usually obtained in 12 - 24 hours. Thereafter dosage may be reduced after 2 - 4 days and gradually discontinued after 5 - 7 days. In patients with recurrent or inoperable neoplasms, maintenance therapy may be effective at doses of 2mg i.m. or i.v.
2 -3 times daily.
High doses of the injection are recommended for initiation of short term intensive therapy in life threatening cerebral oedema. Doses are subsequently scaled down, eventually reducing to zero, over a seven to ten day period (see table). When maintenance therapy is required, injection should be substituted by tablets as soon as possible.

Suggested high dose therapy in cerebral oedema (not vasogenic)

Adults:

Initial dose	50mg intravenous
1st day	8mg intravenous every 2 hours
2nd day	8mg intravenous every 2 hours
3rd day	8mg intravenous every 2 hours
4th day	4mg intravenous every 2 hours
5th - 8th days	4mg intravenous every 4 hours
Thereafter	decrease by daily reduction of 4mg

Paediatric population (Body weight 35Kg and greater)

Initial dose	25mg intravenous
1st day	4mg intravenous every 2 hours
2nd day	4mg intravenous every 2 hours
3rd day	4mg intravenous every 2 hours
4th day	4mg intravenous every 4 hours
5th - 8th days	4mg intravenous every 6 hours
Thereafter	decrease by daily reduction of 2mg

Paediatric population (Body weight less than 35Kg)	
Initial dose	20mg intravenous
1st day	4mg intravenous every 3 hours
2nd day	4mg intravenous every 4 hours
3rd day	4mg intravenous every 4 hours
4th day	4mg intravenous every 6 hours
5th - 8th days	2mg intravenous every 6 hours
Thereafter	decrease by daily reduction of 1mg

Intrasynovial/intralesional/soft tissue injection: Use only when one or two joints affected. Suggested doses are in the table below:

Site of injection	*Dexamethasone phosphate*
Large joint	2mg - 4mg (0.5ml - 1ml)
Small joint	0.8mg - 1mg (0.2ml - 0.25ml)
Bursae	2mg - 3mg (0.5ml - 0.75ml)
Tendon sheath	0.4mg - 1mg (0.1ml - 0.25ml)
Infiltration of soft tissue	2mg - 6mg (0.5ml - 1.5ml)
Ganglia	1mg - 2mg (0.25ml - 0.5ml)

Injections should be done once every three to five days to once every two to three weeks, dependent upon the response of the patient.

Paediatric population

Dosage requirements are variable and may have to be changed according to individual need. Usually 200micrograms/kg to 400 micrograms/kg body weight daily are used.

Use should be limited to a single dose on alternate days in order to minimise suppression of hypothalamo-pituitary-adrenal axis. Also, treatment should be limited to the minimum dosage for the shortest possible time.

If possible this pattern should be used in adults as well.

Elderly

Treatment, particularly if long term, must be planned to avoid more serious consequences of the common side effects in old age. Of especial concern are osteoporosis, diabetes mellitus, hypokalaemia, hypertension, susceptibility to infection and skin thinning. Very close clinical supervision is required.

Method of administration

Dexamethasone solution for injection may be administered intravenously, subcutaneously, intramuscularly or by local injection.
Intra-articular injections should be given under strictly aseptic conditions.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Systemic infection, unless specific anti-infective therapy is also used concomitantly.
In bacteraemia, systemic fungal infection, unstable joints, infection at injection site (i.e septic arthritis resulting from gonorrhoea or tuberculosis) local injection is contraindicated.
Where use of glucocorticoids may be life-saving, contraindications do not usually apply.
Dexamed contains benzyl alcohol and thus it must not be given to premature babies or neonates.

4.4. Special warnings and precautions for use

Undesirable effects can be minimised by use of the lowest effective dose for minimum period, and by administration of daily dose as a single morning dose, or, if possible, as a morning dose on alternate days. It is necessary to frequently review patients to titrate the dose against disease activity.

During prolonged therapy, adrenal cortical atrophy develops. This may persist for years after therapy cessation. Withdrawal of corticosteroids in prolonged therapy must always be gradual to prevent acute adrenal insufficiency. Dosage should be tapered off over weeks or months, depending upon dose and duration of therapy. In prolonged therapy, any inter-current illness, surgical procedure or trauma will require a temporary increase in dosage. If prolonged therapy has stopped, temporary reintroduction of corticosteroids may be necessary.
It is recommended that patients carry a “Steroid Treatment Card”. This should give clear guidance on precautions to minimise risk and provide full details on this medicine, dose, prescriber, treatment duration and necessary precautions to minimize the risk.

The inflammatory response and immune function are suppressed, increasing susceptibility to, and severity of infection. The clinical presentation of infection (i.e tuberculosis, septicaemia) may be latent and may reach an advanced stage before being diagnosed. Appropriate anti-microbial therapy should accompany glucocorticoid therapy when necessary.
Of particular concern is chickenpox, as this usually minor illness may be fatal in immunosuppressed patients. Patients or parents of children, without a definite history of chickenpox must be advised to avoid close personal contact with chickenpox or herpes zoster. If exposure occurs, urgent medical attention must be sought. Exposed non-immune patients on systemic corticosteroids, or who have used

them in the preceding three months, need passive immunisation with varicella zoster immunoglobulin, this should be administered within ten days of exposure. In the case of a confirmed diagnosis of chickenpox, this needs specialist care and urgent medical treatment. Corticosteroids should not be stopped and an increase in dose may be necessary.
Individuals with impaired immune response should not be given live vaccines, and the antibody response to other vaccines may be reduced.

False negative results may occur with the nitroblue tetrazolium test of bacterial infection.

In patients with the following conditions, particular care is needed when considering the use of systemic corticosteroids, and frequent patient monitoring is necessary:

- osteoporosis, note that post menopausal women are particularly at risk
- existing, or previous history of, severe affective disorders, especially steroid psychosis
- glaucoma, or a family history of glaucoma
- renal insufficiency, chronic renal failure
- peptic ulceration
- parasitic infestation, especially amoebiasis
- Cushing's syndrome patients
- Hypothyroidism or cirrhosis
- Previous corticosteroid induced myopathy
- hypertension or congestive heart failure
- diabetes mellitus, or a family history of diabetes
- liver failure
- epilepsy
- migraine
- incomplete natural growth as prolonged administration of glucocorticoids may speed up epiphyseal closure
- Latent tuberculosis
- Latent amoebiasis
- ocular herpes simplex

Paediatric population

In children, corticosteroids cause dose related growth retardation in infancy, childhood and adolescence. This may be irreversible. Growth and development of infants/children on long term corticosteroid therapy must be carefully monitored.

In the elderly, common adverse effects of systemic corticosteroid therapy may be associated with more severe consequences, especially in respect to osteoporosis, hypokalaemia, hypertension, diabetes, skin thinning and infection susceptibility. Close clinical supervision and observation is essential in this group of patients.

In local treatment by injection of conditions such as tendinitis or tenosynovitis, care must be taken to inject into the space between the tendon and the tendon sheath as cases of ruptured tendon have been reported.

Intra – articular corticosteroids are associated with increased risk of an inflammatory response in the joint, particularly a bacterial infection introduced with the injection.
All intra-articular corticosteroid injections should be undertaken in an aseptic environment. Charcot like arthropathies have been reported particularly after repeated injections.
Prior to intra-articular injection the joint fluid should be examined to exclude a septic process. A marked increase in pain, accompanied by local swelling, further restriction of joint motion, fever and malaise are suggestive of septic arthritis. If this complication occurs and sepsis is confirmed, appropriate antimicrobial therapy should be commenced.
Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained but the inflammatory process remains active.

Especially in patients with a history of allergy, serious anaphylactoid reactions have occurred following glucocorticoid administration. These have included glottis oedema, bronchospasm and urticaria. If anaphylactoid reaction occurs, it is recommended to use immediate slow intravenous injection of 0.1ml - 0.5ml adrenaline solution 1:1000 (0.1mg - 0.5mg adrenaline dependent upon body weight), aminophylline intravenous, and artificial respiration if required.

The slower rate of absorption after intramuscular injection should be noted.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

<u>Visual disturbance</u>
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Dexamed contains benzyl alcohol and thus it must not be given to premature babies or neonates. It may cause toxic reactions and allergic reactions in infants and children up to 3 years.

4.5. Interactions with other medicinal products and other forms of interaction

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

The metabolism of corticosteroids is enhanced by liver enzyme inducing drugs such as aminoglutethimide, carbamazepine, ephedrine, barbiturates (phenobarbitone), phenylbutazone, phenytoin, primidone, rifabutin, rifampicin, thus its therapeutic effect may be reduced.

Corticosteroids antagonise the desired effects of anti-hypertensives, diuretics and hypoglycaemic drugs (including insulin).

The hypokalaemic effects of acetazolamide, carbenoxolone, loop diuretics and thiazide diuretics are enchanced by corticosteroids. An increase in dosage requirement for hypoglycaemic drugs (including insulin) may be needed.

Patients receiving corticosteroids and potassium depleting diuretics and/or cardiac glycosides, should be monitored for hypokalaemia. This is of particular importance in patients receiving cardiac glycosides since hypokalamia increases the toxicity of these drugs. The effects of anti-hypertensive drugs are also antagonized by corticosteroids.

Concurrent corticosteroid therapy may enhance the efficacy of coumarin anticoagulants, close monitoring of INR or prothrombin time is necessary to avoid spontaneous bleeding.

Corticosteroids increase salicylate renal clearance; salicylate intoxication may result from steroid withdrawal.

Close monitoring of patients on non-steroidal anti-inflammatory drugs is advised as the incidence and/or severity of gastro-intestinal ulceration may increase.

4.6. Fertility, pregnancy and lactation

Pregnancy

Dexamethasone readily crosses the placenta. In pregnant animals there is evidence of abnormalities of foetal development including intra-uterine growth retardation, small increased risk of cleft palate and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However when administered for prolonged periods or repeatedly during pregnancy corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may in theory occur in the neonate following prenatal exposure to

the corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks.
If corticosteroids are essential, patients with normal pregnancies may be treated as normal. Close monitoring is needed for pregnancies with pre-eclampsia or fluid retention. There is evidence of harmful effects on pregnancy in animals. Infants born to mothers who have received substantial doses of corticosteroids during the pregnancy should be carefully observed for signs of adrenal insufficiency.

Breast-feeding
Small amounts of corticosteroids are excreted in breast milk, although no data are available for dexamethasone. Infants of breast feeding mothers on high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression. Suppression of growth or other adverse effects may occur.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

The following adverse effects with dexamethasone are listed below by system organ class; the frequency is not known (cannot be estimated from available data).

The frequency of predictable undesirable effects, including suppression of hypothalamic-pituitary-adrenal system, correlates with dosage, drug potency, timing of dose and treatment duration (see section 4.4).

High doses of dexamethasone sodium phosphate are intended for short term therapy and therefore adverse reactions are uncommon. However, peptic ulceration and brochospasm may occur.

With the injection only, local adverse reactions include post injection flare, painless destruction of the joint (similar to Charcots arthropathy) especially with repeated intra-articular administration. Local injections may produce systemic effects.

Blood and lymphatic system disorders: leucocytosis

Immune system disorders: severity and susceptibility to infection increased with suppression of clinical symptoms and signs, recurrence of dormant tuberculosis and opportunistic infections. Decrease in response to vaccination and skin tests (see section 4.4).

Endocrine disorders: hypothalamic-pituitary-adrenal axis suppression, suppression of growth (infancy/childhood/adolescence), irregular menstruation and amenorrhoea. Cushinoid syndrome, hirsutism, premature epiphyseal closure, weight gain, carbohydrate tolerance impairment and increased anti-diabetic therapy requirement, impaired glucose tolerance and hyperglycaemia. Increased appetite. Negative calcium and protein/nitrogen balance. Secondary adrenocortical unresponsiveness, particularly in times of stress as in surgery or trauma.

Psychiatric disorders: mental disturbances, psychiatric disturbance which can range from euphoria to frank psychotic manifestations, aggravation of schizophrenia, depression and psychological dependence.

Nervous system disorders: Insomnia, headache, convulsions, vertigo. In children, usually after treatment withdrawal, increased intra-cranial pressure with papilloedema (pseudotumour cerebri). Epilepsy aggravation.

Eye disorders: intra-ocular pressure elevation and posterior subcapsular cataracts may result in glaucoma, or occasionally damage to the optic nerve, papilloedema, corneal or scleral thinning, worsening of opthalmic viral or fungal infection. Chorioretinopathy. Vision, blurred (see also section 4.4).

Vascular disorders: hypertension, thromboembolism

Gastrointestinal disorders: dyspepsia, peptic ulceration (with perforation and haemorrhage), oesophageal ulcerations, acute pancreatitis, candidiasis, abdominal distension and vomiting.

Skin and subcutaneous tissue disorders: acne, bruising, impaired wound healing, skin atrophy, striae, telangiectasia. Petechiae and ecchymoses, erythema, increased sweating, burning or tingling, allergic dermatitis, candidiasis, urticaria, possible suppression of skin tests.

Musculoskeletal and connecting tissue disorders: osteoporosis, fractures of long bones and vertebra, avascular osteonecrosis, tendon rupture and proximal myopathy. Muscle weakness, premature epiphyseal closure, muscular atrophy.

General disorders and administration site conditions: hypersensitivity - including anaphylaxis. Blindness associated with intralesional therapy around the face and neck, hyperpigmentation, hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, post injection flare (following intra-articular injection): Charcot-like arthropathy.

Investigations: sodium and water retention with oedema, nitrogen depletion, hypokalaemic alkalosis, potassium and calcium loss.

Withdrawal symptoms/signs: following prolonged treatment, too rapid dosage reduction of corticosteroid can cause acute adrenal insufficiency, hypotension and death. A withdrawal syndrome may occur, including arthralgia, conjunctivitis, fever, myalgia, painful and itchy skin nodules, rhinitis and weight loss.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA – axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 6 mg dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups gradual withdrawal of systemic corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years)
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy
- Patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone
- Patients repeatedly taking doses in the evening

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy / phs Fax: + 357 22608649.

4.9. Overdose

Definition of overdose is difficult as therapeutic dose varies widely according to indication and patient response. In overdose it would be anticipated that corticosteroid adverse effects would be severe and greater. Treat anaphylaxis with adrenaline and positive pressure ventilation. Symptomatic and supportive treatment is recommended to maintain the patient unstressed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, plain, Glucocorticoids
ATC Code: H02AB02.

Dexamethasone is a synthetic glucocorticoid with an anti-inflammatory potency about seven fold that of prednisolone. As with other glucocorticoids, dexamethasone also possesses anti-allergic, antipyretic and immunosuppressive properties.
It acts on the HPA at specific receptors on the plasma membrane. It diffuses across cell membranes in other tissues and following complexation with specific cytoplasmic receptors, enters the cell nucleus and stimulates protein synthesis.
It has practically no water and salt retaining properties, making it useful in patients with cardiac failure or hypertension. The long biological half-life (36h - 54h) makes it suitable for use in conditions where continuous glucocorticoid action is wanted.

5.2. Pharmacokinetic properties

Generally corticosteroids are well absorbed from the gastro-intestinal tract. Following administration of dexamethasone sodium phosphate, it is rapidly hydrolysed to dexamethasone. Reported plasma half-life is 190 minutes in adults. Intravenous administration gives a rapid onset of action of comparatively short duration. Intramuscular administration results in a slower onset of action with a comparatively longer duration. For this reason the intravenous route is the route of choice in initial dosage in life threatening situations, with maintenance being more appropriate by intramuscular administration.

Corticosteroids are rapidly distributed to all body tissues, they cross the placenta and are excreted in small quantities in breast milk. In the circulation it is extensively bound to plasma proteins, the majority to globulin (high affinity, low capacity) and less so to albumin (low affinity, high capacity). The plasma binding is proportionate to the dose, and in very high doses the majority is unbound. In hypoalbuminaemia the proportion of unbound dexamethasone increases.
Metabolism is mainly in the liver, but also in the kidney, excretion is mainly in urine as unconjugated steroids. Impaired renal function does not significantly influence the elimination of dexamethasone, whereas impaired hepatic function will prolong the elimination half-life in severe impairment.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Solution contains methyl 4-hydroxybenzoate and propyl 4-hydroxybenzoate, sodium chloride, disodium hydrogen phosphate dodecahydrate, sodium citrate dihydrate, benzyl alcohol, disodium edetate, sodium hydroxide and water for injection.

6.2. Incompatibilities

None known.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store below 30^{o}C, in the original package. Do not refrigerate or freeze.

6.5. Nature and contents of container

Amber type I ampoules containing one (1) or two (2) millilitres of solution in a carton containing either 5, 10 or 100 ampoules.

6.6. Special precautions for disposal and other handling

For the injection: use only sodium chloride injection or dextrose injection as the diluent. Infusion solutions must be used within 24 hours.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011, Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

13416

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorization: 26.06.1991
Date of latest renewal: 30.07.2013

10. DATE OF REVISION OF THE TEXT

09/2017