Public Assessment Report

Dexamethasone 2mg Tablets

Dexamethasone

PL 17507/0053

Auden Mckenzie Limited

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Lay Summary

The MHRA has granted Auden Mckenzie Ltd a marketing authorisation (licence) for the medicinal product Dexamethasone 2mg Tablets on 8/12/2006. It is a prescription only medicine. The applicant demonstrated that Dexamethasone 2mg Tablets are a generic medical product of Dexamethasone 2.0mg (PL 00065/5045R, granted 29th March 1990), marketed by Organon Laboratories Ltd

The active ingredient of the product is dexamethasone. Dexamethasone is an anti-inflammatory corticosteroid. It is also used in the prevention of nausea and vomiting induced by cancer chemotherapy.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Dexamethasone 2mg Tablets outweigh the risks, hence a marketing authorisation was granted.

SCIENTIFIC DISCUSSION

Introduction

Based on a review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Dexamethasone 2mg Tablets (PL 17507/0053) to Auden McKenzie Limited on 8/12/2006. The product is a prescription only medicine.

The applicant successfully claimed that the product was a generic medical product of Dexamethasone 2.0mg (PL 00065/5045R, granted 29th March 1990), marketed by Organon Laboratories Ltd under article 10.1. The products contain the same amount of active substance in the same pharmaceutical form. The reference product was a licence of right. The UK brand leader is used in the bioequivalence study.

Dexamethasone is a corticosteroid with mainly glucocorticoid activity; 750 micrograms of dexamethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. Dexamethasone is given intravenously and orally for the prevention of nausea and vomiting induced by cancer chemotherapy. For administration by mouth dexamethasone is given in usual doses of 0.5 to 10 mg daily. Dexamethasone is also used by mouth in the dexamethasone suppression tests for the diagnosis of Cushing's syndrome.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active dexamethasone is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 60 months, stored below 25ºC and protected from light

DRUG PRODUCT

Other Ingredients

The other constituents of Dexamethasone 2mg Tablets are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), colloidal hydrated silica, magnesium stearate (E470b). Lactose is sourced from milk produced by healthy cows and magnesium stearate is of vegetable origin. All these ingredients are controlled to Ph Eur monographs.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to those for the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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

1. PVC/Aluminium blister strips of 10 tablets
    - Rigid white PVC film; gauge 0.250 mm ± 5%.
    - Aluminium 0.020mm hard. Matt side: clear, heat-resistant print primer; bright side: heatseal lacquer to seal to PVC. Total weight: 62.5 g/sq m ± 10%
    - 5 (50s) or 10 (100s) blister strips per preprinted cardboard cartons
2. Tablet Containers (500s)
    - White, straight-sided polypropylene container bottles (130ml capacity) with polypropylene Snap-Secure caps.

Satisfactory specifications, test performed and results of tests were provided for packaging materials. Packaging conforms to Directive 2002/72/EC.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Protect from light”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No preclinical data were submitted with this application and none were required.

MEDICAL ASSESSMENT

Clinical Pharmacology

General

The adrenal cortex synthesises corticosteroids. Corticosteroids are traditionally divided into those with predominantly glucocorticoid actions and those of which the actions are primarily mineralocorticoid. The endogenous glucocorticoids are under regulatory control from the hypothalamus and pituitary via releasing hormones. In return, the glucocorticoids act to inhibit production and release of the releasing hormones by a negative feedback mechanism. Glucocorticoid actions are wide ranging. They have potent anti-inflammatory and immunosuppressive effects, achieved at least partly through inhibition of various cytokines. It is primarily these effects which are made use of clinically. Glucocorticoids also have profound metabolic effects on blood glucose concentration, glycogen deposition, protein breakdown, lipolysis and effects on calcium uptake and excretion. They also have effects on the function of the cardiovascular system, kidneys, skeletal muscle and the CNS.

Dexamethasone is a synthetic glucocorticoid of which the anti-inflammatory potency on a weight for weight basis is 7 times greater than that of prednisolone. Pharmacological doses of corticosteroids/glucocorticoids are used when palliative anti-inflammatory or immunosuppressant effects are required to suppress the clinical manifestations of disease in a wide range of disorders considered to have inflammatory or immunological components.

Lack of mineralocorticoid (water and salt-retaining) properties makes dexamethasone particularly suitable for treating conditions where water retention would be a disadvantage, for example, cerebral oedema. Coupled with its long duration of action, dexamethasone is also indicated for conditions such as congenital adrenal hyperplasia which require suppression of corticotrophin secretion.

Pharmacokinetic properties

Dexamethasone is readily absorbed from the gastrointestinal tract. Corticosteroids are rapidly distributed to all body tissues. They cross the placenta and may be excreted in small amounts in breast milk. Corticosteroids bind extensively to plasma proteins, though the synthetic ones are less extensively protein bound than cortisol. They also tend to have longer half-lives; the biological half-life of dexamethasone in plasma is 3-4 hours. Corticosteroids are metabolised mainly in the liver but also in other tissues and are excreted in the urine.

The slower metabolism and lower protein-binding affinity of the synthetic corticosteroids compared with the natural corticosteroids may account for their increased potency.

Bioequivalence Study

The applicant supplied a bioequivalence study comparing their generic dexamethasone 2mg tablets (test) to the reference product manufactured by Organon.

This was a randomised, open-label, single-dose, two-way crossover trial in fasted male healthy volunteers.

Volunteers received both treatments in a randomised order, receiving a single dose in each of two study periods, the periods being separated by a washout period of 4 days. Blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24 hours after dosing.

Subject accountability

There were 30 subjects randomised into the trial. There were 4 subjects who were withdrawn before the first study period began. Subject 2 withdrew consent, while subjects 8, 14 and 30 were found to have pre-existing medical conditions that precluded their involvement. One further subject experienced an adverse event during study period 1 and was withdrawn from the study. This left 25 subjects who completed both study periods and were included in the analysis.

It is appropriate to exclude patients who don't complete both study periods from the analysis.

Results

The percentage of $AUC_{0-\infty}$ which was extrapolated was less then 20% in both periods for all but 2 subjects (subject 27 on reference, subject 16 on test) indicating that the sampling schedule was sufficient to characterise the concentration curves.

There were no subjects with positive plasma concentrations at the start of period 2, so the washout period was of an adequate duration.

	Geometric mean		Ratio: Test/Reference	
Parameter	Test	Reference	Point estimate	90% CI
AUC_{0-t} (ng.h/mL)	145.96	145.91	1.00	0.96-1.05
$AUC_{0-\infty}$(ng.h/mL)	167.08	163.70	1.02	0.98-1.06
C_{max} (ng/mL)	21.43	24.73	0.87	0.81-0.93

The confidence intervals are contained within 0.80-1.25 for all three parameters.

There were 2 subjects who had a missing observation in their plasma data. These were subjects 15 and 23, both while using the reference product. The relevant measurements for these subjects are shown in the table below.

Time-point (hrs)	Subject 15 (test)	Subject 15 (reference)	Subject 23 (test)	Subject 23 (reference)
0	0	0	0	0
0.25	2.417	2.772	0	0
0.5	12.445	18.206	4.871	0
0.75	22.565	Missing	8.514	3.690
1.00	21.611	24.561	8.717	10.899
1.25	19.336	20.139	12.105	Missing
1.50	22.600	20.012	11.471	17.192
1.75	18.609	19.404	11.240	17.151
2	18.839	17.400	10.512	15.556
2.5	16.603	14.497	8.340	15.206
3	16.641	14.182	11.046	13.052
4	12.223	13.607	9.210	13.275
5	10.202	13.293	8.368	10.317
6	8.742	10.958	4.804	10.057
7	7.661	9.107	5.778	7.232

It is a possibility that the missing value is C_{max} for one or both of these patients. The lower bound of the current confidence interval for C_{max} is close to 0.80, with the test formulation generally having a lower C_{max}. If the missing data did represent the C_{max} in these cases, the average reference C_{max} would become still higher, and it is possible that the confidence interval could fall below 0.80.

The statistical assessor investigated what the missing values would have to be for the confidence interval for relative C_{max} to fall below 0.80-1.25.

Example C_{max} values where lower bound goes below 0.80

Subject 15	Subject 23
35.40	17.19 (unchanged)
24.56 (unchanged)	22.27
29.10	20.37

From the statistical assessor's calculations, if the reference C_{max} for subject 15 exceeded 35.40 then the lower bound of the confidence interval would move below 0.80. This would also happen if the reference C_{max} for subject 23 exceeded 22.27. Another example would be if the value for subject 15 exceeded 29.10 and for subject 23 exceeded 20.37.

The necessary differences between C_{max} and the next largest value would be large, so it seems that the conclusion of bioequivalence for C_{max} is fairly robust to this missing data, even though the lower bound of the interval is close to 0.80.

The confidence intervals for all 3 parameters are contained within 0.80-1.25, supporting the conclusion that the test 2mg tablet is bioequivalent to the reference.

Although 2 patients had missing data that potentially effect the calculation of C_{max}, the conclusions seem fairly robust.

Conclusion

The primary bioequivalence parameters Cmax, AUC_{0-t} and AUC_{∞} are within the acceptable limits. Bioequivalence has been demonstrated between the product and the reference product.

Clinical Efficay

The applicant has not submitted a clinical efficacy study with this application. This is considered appropriate as the efficacy of dexamethasone is well recognised.

Clinical Safety

No new data submitted. The safety profile of dexamethasone is well recognised. The clinical expert presents a review of possible impurities or decomposition products affecting safety.

Product Literature

Satisfactory Summary of Product Characteristics, Patient Information Leaflet and Labels were provided.

Conclusion

A marketing authorisation was granted for this product.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Dexamethasone 2mg 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.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

Bioequivalence has been demonstrated between the applicant's Dexamethasone 2mg Tablets and the reference product. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 16/08/2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 13/09/2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 26/05/2006 and on the medical assessment on 30/06/2006 and 03/07/2006
4	The applicant provided further information in regard to the quality assessment on 03/07/2006 and on the medical assessment on 03/07/2006 and 06/11/2006.
5	The application was determined on 08/12/2006.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone 2mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.0 mg dexamethasone.
Contains lactose monohydrate (68.8mg per tablet); for a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Round white tablet, one side marked DX 2

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated in a wide variety of disorders amenable to glucocorticoid therapy, as well as an adjunct in the control of cerebral oedema.

4.2 Posology and method of administration

In general, glucocorticoid dosage depends on the severity of the condition and response of the patient. Under certain circumstances, for instance in stress and changed clinical picture, extra dosage adjustments may be necessary. If no favourable response is noted within a couple of days, glucocorticoid therapy should be discontinued.

1. *Adults*

   Usually, daily oral dosages of 0.5 - 10 mg are sufficient. In some patients higher dosages may be temporarily required to control the disease. Once the disease is under control, the dosage should be reduced or tapered off to the lowest suitable level under continuous monitoring and observation of the patient. **(See Section 4.4)**

   For a short dexamethasone suppression test, 1mg dexamethasone is given at 11 pm and plasma cortisol measured the next morning. Patients who do not show a decrease in cortisol can be exposed to a longer test: 500 micrograms dexamethasone is given at 6 hourly intervals for 48 hours followed by 2mg every 6 hours for a further 48 hours. Twenty-four hour urine collections are

made before, during and at the end of the test for determination of 17-hydroxycorticosteroids.

2. *Children*

   0.01-0.1mg/kg of body weight daily

   Dosage of glucocorticoids should be adjusted on the basis of the individual patient's response.

4.3 Contraindications

Systemic infection unless specific antimicrobial therapy given; avoid live virus vaccines in those receiving immunosuppressive doses as the serum antibody response is diminished.

In general, no contraindications apply in conditions where use of glucocorticoids may be life saving.

4.4 Special warnings and precautions for use

Every patient should receive the patient information leaflet.

Patients on long-term dexamethasone treatment should carry a Steroid Treatment Card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

Adrenal Suppression

Abrupt withdrawal after prolonged therapy with corticosteroids may lead to acute adrenal insufficiency, hypotension or death.

During prolonged therapy with corticosteroids, adrenal atrophy develops and may persist for years after stopping. Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. Anaesthetists must therefore know whether a patient is taking or has been taking a corticosteroid, to avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period. A suitable regimen for corticosteroid replacement, in patients who have taken more than 1.5 mg dexamethasone daily within 3 months of surgery, is:

- *Minor surgery under general anaesthesia*—usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25–50 mg (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery
- *Moderate or major surgery*—usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25–50 mg intravenously at induction, followed by hydrocortisone 25–50 mg 3 times a day by intravenous

injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections.

Infections
Prolonged courses of dexamethasone increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. septicaemia and tuberculosis may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating dexamethasone in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated. Appropriate anti-microbial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye.
CHICKENPOX
Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid personal contact with chickenpox or herpes zoster and if exposed, they should seek urgent medical attention.
Unless they have had chickenpox, patients receiving oral dexamethasone for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature.
Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non-immune patients currently taking dexamethasone tablets or for those who have used them within the previous 3 months; varicella–zoster immunoglobulin should preferably be given within 3 days of exposure and no later than 10 days. Confirmed chickenpox warrants specialist care and urgent treatment. Dexamethasone should not be stopped and dosage may need to be increased.
MEASLES
Patients taking dexamethasone should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Infants, Children and adolescents
Growth retardation - possibly irreversible

Elderly
Close supervision required particularly on long-term treatment

The common adverse events of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close supervision is required to avoid life-threatening reaction.

Frequent monitoring is required in the following situations:

- history of tuberculosis (or X-ray changes)
- hypertension
- recent myocardial infarction (rupture reported)
- congestive heart failure
- renal impairment
- diabetes mellitus including family history
- osteoporosis (post-menopausal women at special risk)
- glaucoma (including family history)
- corneal perforation
- severe affective disorders (particularly if history of steroid-induced psychosis)
- epilepsy
- peptic ulcer
- hypothyroidism
- history of steroid myopathy

Withdrawal of dexamethasone
Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids must therefore always be gradual to avoid adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg of 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 1mg dexamethasone is reached, dose reduction should be slower to allow the HPA axis to recover.

The Committee on Safety of Medicines has recommended that gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have

- recently received repeated courses (particularly if taken for longer than 3 weeks)
- taken a short course within 1 year of stopping long-term therapy
- other possible causes of adrenal suppression
- received more than 6mg dexamethasone daily
- been given repeat doses in the evening
- received more than 3 weeks' treatment

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological-equivalent doses – approximately 1mg dexamethasone daily and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

Patients with rare heredity 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

Dexamethasone may interact with other products as follows:

Product	Effect
Aprepitant:	metabolism of dexamethasone inhibited therefore reduce dose of dexamethasone
Caspofungin:	dexamethasone possibly reduces plasma concentration of caspofungin; consider increasing dose of caspofungin
Ephedrine:	metabolism of dexamethasone accelerated
Indinavir) Lopinavir) Saquinavir)	dexamethasone possibly reduces plasma concentration
Ritonavir:	plasma concentration of dexamethasone possibly increased

As dexamethasone is a **Corticosteroid,** the following interactions could occur:

Product	Effect
ACE Inhibitors) Adrenergic neurone blockers) Alpha-blockers) Angiotensin-II Receptor Agonists) Beta-blockers) Calcium-channel blockers) (Dihydropyridine calcium-channel blockers include amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine) Clonidine) Diazoxide) Hydralazine) Methyldopa) Minoxidil)	antagonism of hypotensive effect

Moxonidine	)	
Nitrates	)	
Nitroprusside	)	
Acetazolamide	)	
Amphotericin*	)	
Carbenoxolone	)	
Cardiac Glycosides	)	increased risk of hypokalaemia
Diuretics, Loop	)	
Diuretics, Thiazide and Related	)	
Theophylline	)	
β-Sympathomimetics (high dose)	)	monitor plasma K in severe asthma
Aminoglutethimide	)	
Barbiturates*	)	
Carbamazepine*	)	metabolism of corticosteroids
Phenytoin*	)	accelerated (reduced effect)
Primidone*	)	
Rifamycins*	)	

Amphotericin* avoid concomitant use unless amphotericin needed to control reactions; close monitoring required – amphotericin nephrotoxic

Antidiabetics	antagonism of hypoglycaemic effect

Aspirin	)	increased risk of gastro-intestinal
NSAIDs	)	bleeding and ulceration

Aspirin corticosteroids reduce plasma concentration of salicylate

Coumarins* corticosteroids may enhance or reduce anticoagulant effect of coumarins (high-dose corticosteroids enhance anticoagulant effect)

Diuretics	antagonism of diuretic effect

Erythromycin)	metabolism of corticosteroids
Ketoconazole)	possibly inhibited

Methotrexate*	increased risk of haematological toxicity

Mifepristone effect of corticosteroids may be reduced for 3–4 days after mifepristone

Nephrotoxic/Cytotoxic drugs close monitoring required

Oestrogens plasma concentration of corticosteroids increased by oral contraceptives containing oestrogens; low dose in HRT unlikely to induce interactions

Somatropin growth-promoting effect of somatropin may be inhibited

Vaccines* high doses of corticosteroids impair immune response to vaccines; avoid concomitant use with live vaccines. Live vaccines should be postponed until at least 3 months after stopping corticosteroids
* **Potentially hazardous interaction**

4.6 Pregnancy and lactation

Dexamethasone readily crosses the placenta with minimal inactivation but there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip.
Prolonged or repeated administration during pregnancy increases the risk of uterine growth retardation.
Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously and is rarely clinically important.
Systemic effects in the infant are unlikely with a maternal dose of dexamethasone up to 6 mg daily (≡ 40 mg prednisolone); the infant's adrenal function should be monitored with higher doses.

Corticosteroids may be excreted in small amounts in breast milk.
Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Adverse glucocorticoid effects lead to mobilisation of calcium and phosphorus, with osteoporosis and spontaneous fractures. Hyperglycaemia may precipitate or accentuate diabetes leading to an increase in the insulin requirements of diabetic patients.

Apart from osteoporosis which is a danger, particularly in the *elderly,* as it may result in osteoporotic fractures for example of the hip or vertebrae, *musculoskeletal effects* include long bone fractures, tendon rupture and muscle wasting (proximal myopathy). High doses are associated with avascular necrosis of the femoral head.

Mental and neurological disturbances may occur. Euphoria is frequently observed. Other *neuropsychiatric effects* include psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of both schizophrenia and epilepsy. A serious paranoid state or depression with risk of suicide may be induced, particularly in patients with a history of mental disorder.

Gastro-intestinal effects include dyspepsia, abdominal distension, acute pancreatitis, oesophageal ulceration and candidiasis. Corticosteroid therapy is also weakly linked with peptic ulceration.

The negative feedback effects of glucocorticoids on the hypothalmic-pituitary-adrenal axis may lead to adrenal atrophy. This produces secondary adrenal insufficiency which may become manifest following overly rapid withdrawal of treatment or be precipitated by some stress such as infection or trauma. Resultant *endocrine effects* include menstrual irregularities and amenorrhoea, hirsutism, weight gain, negative nitrogen and calcium balance and increased appetite.

High doses of corticosteroids administered during *pregnancy* may cause *foetal or neonatal* adrenal suppression.

Conversely, high doses of corticosteroids may produce the Cushingoid symptoms typical of hyperactivity of the adrenal cortex: moon face; hirsutism; buffalo hump; flushing; increased bruising; ecchymoses; striae; acne. They are usually reversible on withdrawal of treatment, but dosage must always be tapered gradually to avoid symptoms of acute adrenal insufficiency.

Administration of even relatively small doses of corticosteroids to *children* may suppress growth.

Anti-inflammatory and Immunosuppressive Effects
Suppression of clinical symptoms and signs by the anti-inflammatory, analgesic and antipyretic effects of glucocorticoids may mask an increased susceptibility to infection (septicaemia, tuberculosis, fungal and viral infections) and increased severity of infection brought about by the immunosuppressive effects. As a number of cases of fatal or near-fatal cases of chickenpox (varicella) have been reported, passive immunisation should be given to non-immune patients receiving corticosteroids.

Impaired tissue repair and immune function can lead to delayed wound healing,

Other side-effects include skin atrophy, bruising, telangiectasia, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbance, leucocytosis, hypersensitivity reactions (including anaphylaxis), nausea, malaise, hiccups, hyperhidrosis, benign intracranial hypertension,. An increase in coagulability of blood may lead to thromboembolic complications.

Ophthalmic effects include glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease.

The incidence of adverse effects rises steeply if dosage increases much above physiological values, represented by just over 1mg of dexamethasone. Short courses at high doses for emergencies appear to cause fewer side-effects than

prolonged courses with lower doses. Thus, adverse effects are minimised by using the lowest effective dose and for the minimum period possible.

Withdrawal symptoms and signs
Withdrawal should be gradual in those who have been treated for any length of time. Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4).
Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

4.9 Overdose
It is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to indication and patient requirements.

Overdosage or prolonged use may exaggerate glucocorticoid adverse effects. Treatment should be symptomatic and supportive with the dosage of dexamethasone being reduced or slowly withdrawn where possible.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
[ATC Code: H02AB02 Systemic Hormonal Preparations (excluding sex hormones and insulins); Corticosteroids for Systemic Use; Plain; Glucocorticoids; Dexamethasone]

The adrenal cortex synthesises corticosteroids. Corticosteroids are traditionally divided into those with predominantly glucocorticoid actions and those of which the actions are primarily mineralocorticoid. The endogenous glucocorticoids are under regulatory control from the hypothalamus and pituitary via releasing hormones. In return, the glucocorticoids act to inhibit production and release of the releasing hormones by a negative feedback mechanism. Glucocorticoid actions are wide ranging. They have potent anti-inflammatory and immunosuppressive effects, achieved at least partly through inhibition of various cytokines. It is primarily these effects which are made use of clinically. Glucocorticoids also have profound metabolic effects on blood glucose concentration, glycogen deposition, protein breakdown, lipolysis and effects on calcium uptake and excretion. They also have effects on the function of the cardiovascular system, kidneys, skeletal muscle and the CNS.

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required to suppress the clinical manifestations of disease in a wide range of disorders considered to have inflammatory or immunological components.

Lack of mineralocorticoid (water and salt-retaining) properties makes dexamethasone particularly suitable for treating conditions where water retention would be a disadvantage, for example, cerebral oedema. Coupled with its long duration of action, dexamethasone is also indicated for conditions such as congenital adrenal hyperplasia which require suppression of corticotrophin secretion.

5.2 Pharmacokinetic properties

Dexamethasone is readily absorbed from the gastrointestinal tract. Corticosteroids are rapidly distributed to all body tissues. They cross the placenta and may be excreted in small amounts in breast milk. Corticosteroids bind extensively to plasma proteins, though the synthetic ones are less extensively protein bound than cortisol. They also tend to have longer half-lives; the biological half-life of dexamethasone in plasma is 3-4 hours. Corticosteroids are metabolised mainly in the liver but also in other tissues and are excreted in the urine.

The slower metabolism and lower protein-binding affinity of the synthetic corticosteroids compared with the natural corticosteroids may account for their increased potency.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Colloidal hydrated silica
Magnesium stearate (E470b)

6.2 Incompatibilities

None known

6.3 Shelf life

2 years

6.4 Special precautions for storage
Protect from light

6.5 Nature and contents of container
PVC/Aluminium blister strips of 10 tablets in packs of 50 and 100 tablets.
Hospital pack: Polypropylene bottle of 500 tablets with polypropylene Snap-Secure cap.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie Ltd (Pharma Division)
Unit 30, Stadium Business Centre
North End Road
Wembley
Middlesex
HA9 0AT

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/12/2006

10 DATE OF REVISION OF THE TEXT

08/12/2006

Labels and Leaflet

PATIENT INFORMATION LEAFLET

DEXAMETHASONE 2 mg TABLETS

Before this product is used, please read this leaflet carefully as it contains important information. Do not throw it away. You may want to read it again. If you have any further questions, please ask your doctor or pharmacist.
This product has been prescribed for you. You should not pass it on to other people. It may harm them.

Why do you need to take Dexamethasone 2mg Tablets?

Dexamethasone 2mg Tablets are usually used to reduce inflammation and to treat some disorders of the immune system. They may also be useful in helping control swelling on the brain.

How do Dexamethasone 2mg Tablets work?

Dexamethasone is a synthetic steroid (specifically, a corticosteroid) which is a hormone similar to one that our bodies release from the adrenal gland.

Before you take Dexamethasone 2mg Tablets

Do not take the tablets if:

- you have an infection
- you are going to have any vaccinations – you must tell the doctor or nurse that you have been prescribed Dexamethasone 2mg Tablets.
- you are allergic to dexamethasone or any of the other ingredients
- if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

Are you pregnant or breast-feeding?
Tell the doctor if you are pregnant, think you might be pregnant or are trying to become pregnant. Dexamethasone can reach your baby and may slow its growth.
Small amounts of dexamethasone may get into breast milk; tell the doctor if you are breast-feeding.

Take special care:

- if you are going to be on Dexamethasone 2mg Tablets for a long time

  Remember always to carry a **Steroid Treatment Card**; make sure your doctor or pharmacist gives you this and has filled out the details including the dose and how long you will have treatment.

  Taking Dexamethasone 2mg Tablets for a long time increases your chance of getting infections and these might be worse than normal. Also, dexamethasone treatment can hide the usual symptoms of infection. Amoebic dysentery and an infestation of a gut worm (*strongyloidiasis*) may be activated or become worse, as may fungal and viral infections of the eye.
  It is particularly important to **avoid contact** with people who have **chicken pox, shingles** or **measles** especially if you have not already had these illnesses or are not sure if you have had them. Dexamethasone 2mg Tablets increase the risk of a severe bout of chicken pox. You still need to take it but the dose may need adjusting. If you are about to take Dexamethasone 2mg Tablets, or are already taking them, and you get a rash or other symptoms of an infection, tell your doctor immediately as additional treatment may be required. Go to your doctor immediately if you come in contact with measles.

- if you are taking or have recently (within the last 3 months) been taking Dexamethasone 2mg Tablets and you become ill, suffer stress, get injured or are about to have surgery. Tell your doctor or other healthcare professional.

- if you need a vaccination (e.g. for a holiday abroad), make sure you tell your doctor as you may not be able to have certain vaccinations.

- if you have been on Dexamethasone 2mg Tablets and wish to stop taking it, see your doctor or pharmacist.

- if Dexamethasone 2mg Tablets are to be given to a **child or teenager**. Their growth may be slowed down and this effect can continue after stopping treatment.

If you think any of these apply to you, or you are unsure, talk to your doctor and follow the advice given.

You must tell your doctor **if you are elderly or have any of the following:**
- history of tuberculosis (or X-ray changes)
- high blood pressure
- recent heart attack
- heart failure
- kidney disease
- diabetes or a family history of it
- brittle bones (*osteoporosis*); particularly if you are a woman past the menopause
- raised pressure within the eye (*glaucoma*) or a family history of it
- damage to the surface of the eye
- severe behavioural problems or a history of psychosis when taking steroids
- fits (*epilepsy*)
- stomach ulcer
- under-active thyroid
- history of muscle wasting caused by steroids
- migraine
- stunted growth

Taking other medicines
Tell the doctor if you are taking, or have recently taken or used:

- **the antibiotics, amphotericin** or erythromycin
- **blood thinning medicines (*anticoagulants*), particularly warfarin**
- sleeping tablets (***barbiturates***)
- **the anti-epileptic drugs, carbamazepine, phenytoin or primidone**
- the anti-cancer drug, **methotrexate**
- anti-tuberculosis drugs (***rifamycins***)
- a drug used in the treatment of breast cancer (*aminoglutethimide*)
- the antifungal drugs, caspofungin or ketoconazole
- antiviral drugs such as indinavir
- a drug used to treat feeling and being sick, aprepitant
- aspirin or other painkillers (*non-steroidal anti-inflammatory drugs*)
- an ulcer-healing drug, carbenoxolone
- drugs which regulate heart beat such as digoxin
- anti-cancer drugs (*cytotoxics*)
- 'water' tablets (*diuretics*)
- drugs used to treat asthma, ephedrine and theophylline
- blood sugar lowering medicines such as insulin and other antidiabetic drugs
- medicines for lowering blood pressure
- a drug used to assist medical termination of pregnancy, mifepristone
- contraceptive pills
- the growth hormone, somatotropin

- asthma preparations such as salbutamol in high doses
- antacids especially those containing magnesium trisilicate
- any other medicine or remedy, even those you have bought yourself

as Dexamethasone 2mg Tablets may affect how they work, or they may affect how Dexamethasone 2mg Tablets work.

While you take Dexamethasone 2mg Tablets

Driving and using machines
Dexamethasone 2mg Tablets should not affect your ability to drive.

How to take Dexamethasone 2mg Tablets

The dose is chosen by your doctor and usually depends on how serious your condition is. Always follow your doctor's instructions and read the pharmacy label. If you are unsure, ask your doctor or pharmacist.

Your doctor will probably ask you to take between one tablet and 5 tablets DAILY, that is a total daily dose of between 2mg and 10mg. Up to 20mg daily may be given for treating swelling on the brain.

Your doctor will tell you how much to give a child.

Usually, you will take your day's dose of Dexamethasone 2mg Tablets as a single dose in the morning.

Sometimes, you may need blood or urine tests to work out how much you should take.

Swallow the tablets whole with some water. Do not chew them.

Do not stop taking Dexamethasone 2mg Tablets suddenly. When you no longer need them, your daily dose should be reduced gradually. However, you should speak to your doctor or pharmacist about the best way to safely reduce your daily dose.

If you take more Dexamethasone 2mg Tablets than you should:
Taking too many tablets will cause much larger effects and you may get any of the side effects described in this leaflet. Tell your doctor who will treat your symptoms and may slowly reduce your dexamethasone dose. Do not stop taking your Dexamethasone 2mg Tablets suddenly.

If you miss a dose of Dexamethasone 2mg Tablets:
Take it as soon as you remember then continue to take your medicine as before.

Do not stop taking Dexamethasone 2mg Tablets just because you feel better. If you stop too soon or too suddenly you may get withdrawal symptoms which can be severe. Refer to your **Steroid Treatment Card** and always discuss your treatment with your doctor who will tell you if treatment can be stopped and how to reduce the dose gradually.

Sudden withdrawal (after 3 weeks or more of treatment) can cause such a severe drop in blood pressure it may kill you.
Less severe symptoms of withdrawal can include:

- fever, muscle pain, joint pain, runny nose (*rhinitis*), sticky eyes (*conjunctivitis*), painful itchy skin lumps and weight loss

Possible side effects

Like all medicines, Dexamethasone 2mg Tablets can have side effects in some patients.
These can include:

- brittle bones (*osteoporosis*), spontaneous fractures, tendon rupture, muscle wasting

- diabetes, reduced carbohydrate tolerance – increased insulin need
- mental disturbances such as excitability (*euphoria*), delusions (*paranoia*), psychological dependence, depression (risk of suicide in patients with a history of mental disorder), insomnia, psychosis, aggravation of schizophrenia and epilepsy
- indigestion, abdominal bloating, acute pancreatitis, oesophageal ulceration, thrush (*candidiasis*)
- irregular or absent monthly periods, weight gain, increased appetite.
- moon face, excess body hair (hirsutism), flushing, increased bruising and skin discolouration, acne
- stunted growth (infants, children, teenagers)
- increased liability to infection and severity of infection
- delayed wound healing, skin thinning, dilated capillaries, heart muscle rupture subsequent to recent heart attack, changes in fluid levels and the levels of certain chemicals in your blood called electrolytes, increased concentration of white blood cells, allergic reactions (including anaphylaxis), nausea, malaise, hiccups, increased sweating, increased likelihood of blood clots
- increased pressure within brain or eye
- increased severity of eye infections

You are more likely to have side effects if you are on a higher dose.

If you notice the above or any other side effects, tell your doctor or pharmacist.

Keeping Dexamethasone 2mg Tablets

Keep Dexamethasone 2mg Tablets out of the reach and sight of children.
Protect them from light by keeping them in their original container.
There is an expiry date (Month/Year) on the pack. The tablets should not be used after the end of the month shown.

What is in Dexamethasone 2mg Tablets?

The name of your medicine is Dexamethasone 2mg Tablets. As well as containing 2mg of dexamethasone, each tablet contains lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), colloidal hydrated silica and magnesium stearate (E470b).

Dexamethasone 2mg Tablets are round, white tablets, marked DX on one side.

They are supplied in blister packs of 50 and 100 tablets, and a plastic bottle of 500 tablets (Hospital dispensing pack only).

Addresses

Marketing authorisation holder: Auden Mckenzie Ltd (Pharma Division),
Unit 30, Stadium Business Centre, North End Road, Wembley, Middlesex, HA9 0AT.

Manufacturer: TioFarma BV, Benjamin Franklinstraat 9, Oud-Beijerland, The Netherlands

For information in large print, on tape, on CD or in Braille, phone 020 8900 2122.

Date of approval of this leaflet: November 2006

Dexamethasone 2 mg Tablets PL 17507/0053

Auden Mckenzie

AUDEN MCKENZIE (PHARMA DIVISION) LIMITED

Dexamethasone
2mg Tablets
50 tablets
Please affix dispensing label here
5060032240640
Keep out of sight and reach of children.
For oral administration only.
Dose: Use only as directed by a medical practitioner
Also contains lactose monohydrate.
Each tablet contains 2mg Dexamethasone.
Protect from light.
Please read the enclosed leaflet
50 tablets
Dexamethasone
2mg Tablets
50 tablets
POM
2 mg
BN: xxxx
EXP: xx/yyyy
CH637/1
PL No. 17507/0053
Product Licence Holder: Auden Mckenzie (Pharma Division) Ltd.
30 Stadium Business Centre, North End Road,
Middlesex, HA9 0AT, UK.

Dexamethasone
2mg Tablets
100 tablets
Each tablet contains 2mg Dexamethasone.
Also contains lactose monohydrate.
Dose: Use only as directed by a medical practitioner.
For oral administration only.
KEEP OUT OF SIGHT AND REACH OF CHILDREN.
Protect from light.
PL No. 17507/0053
Product Licence Holder: Auden Mckenzie (Pharma Division) Ltd
30 Stadium Business Centre, North End Road, Middlesex, HA9 0AT, UK.
Dexamethasone
2mg Tablets
Please read the enclosed leaflet
100 tablets
Dexamethasone
2mg Tablets
100 tablets
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2 mg
BN : xxxx
EXP : xx/yyyy
Please affix dispensing label here
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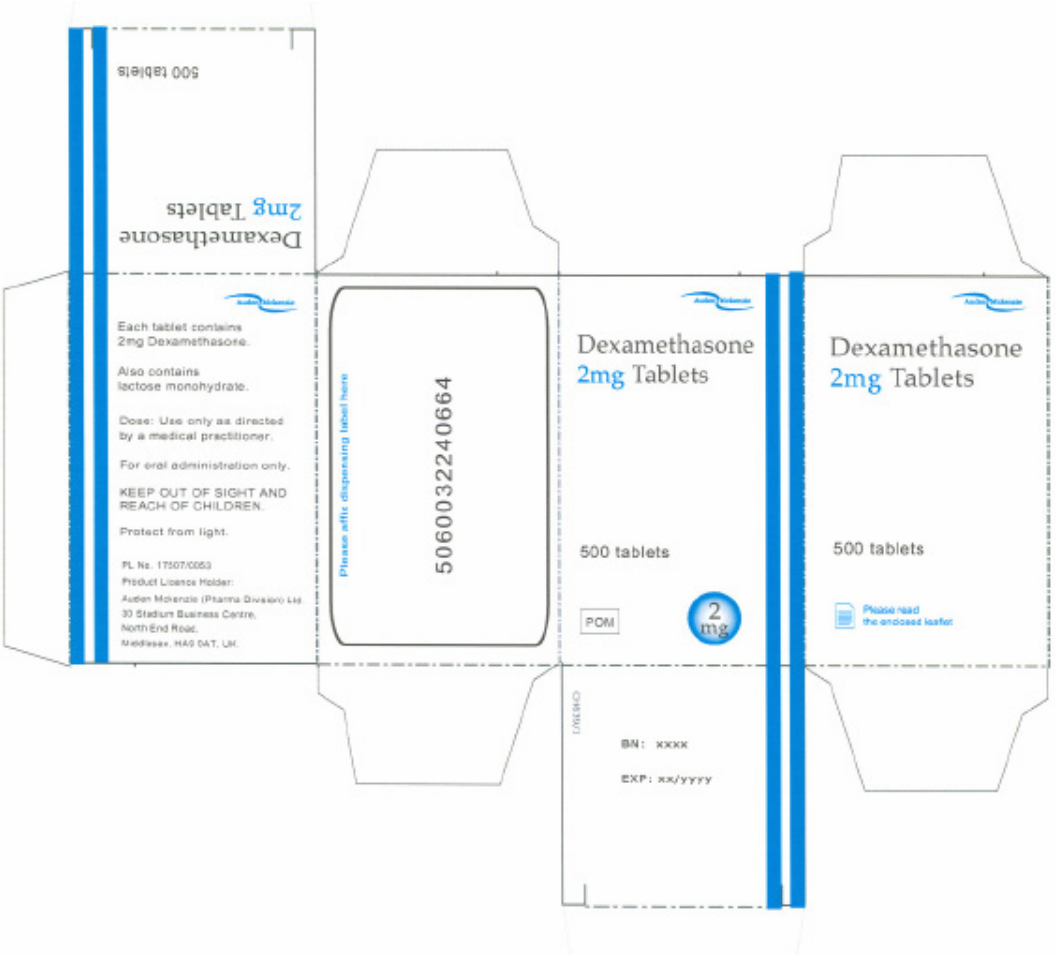
500 tablets
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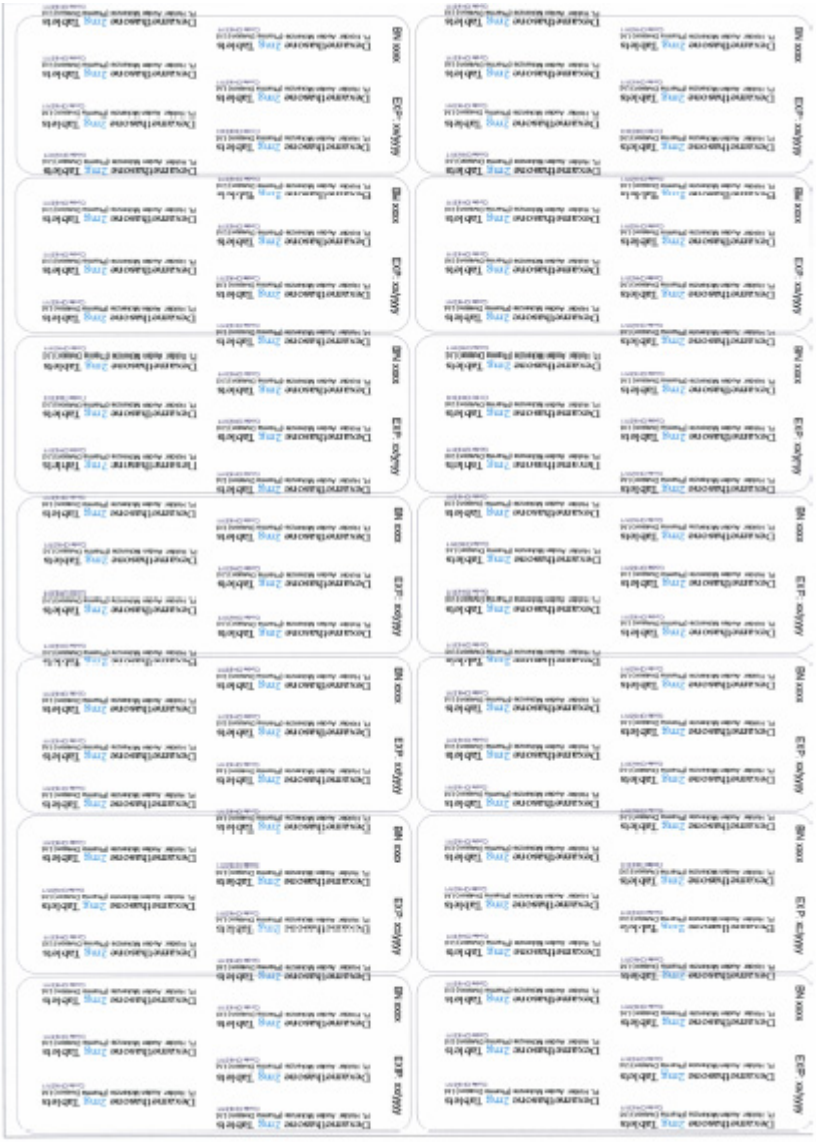
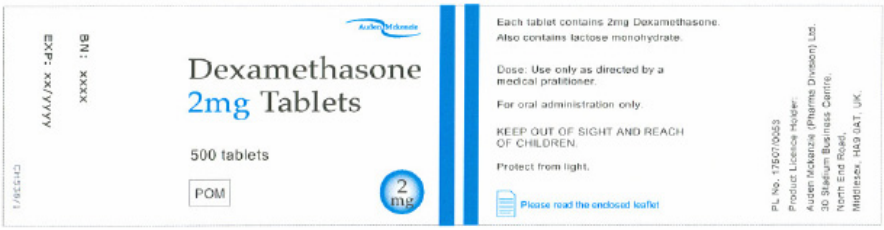
Please affix dispensing label here
5060032240664
Dexamethasone
2mg Tablets
500 tablets
POM
2
mg
BN: xxxx
EXP: xx/yyyy
Dexamethasone
2mg Tablets
500 tablets
Please read
the enclosed leaflet

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