1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BETADEXAMINE TABLETS 0,25 mg/2 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0,25 mg betamethasone and 2 mg dexchlorpheniramine maleate.

Contains sugar: Anhydrous lactose 174,75 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

BETADEXAMINE TABLETS are white to off-white round tablets debossed with A24 on one side and a score line on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

BETADEXAMINE TABLETS are recommended in the treatment of:

- Acute allergic rhinitis, not responsive to conventional therapy.
- Steroid-responsive dermatological allergies and steroid-responsive dermatoses.

4.2. Posology and method of administration

Posology

DOSAGE SHOULD BE INDIVIDUALISED AND ADJUSTED ACCORDING TO THE CONDITION UNDER TREATMENT AND THE RESPONSE OBTAINED.

BETADEXAMINE TABLETS are only to be used for short-term treatment (less than 5 days).

BETADEXAMINE TABLETS should only be used for well-defined indications.

BETADEXAMINE TABLETS should not be mixed with other mixtures.

Adults

The recommended initial dosage for adults and children over 12 years is 1 (one) to 2 (two) tablets four times daily after meals and at bedtime. The dose is not to exceed 8 (eight) tablets per day.

As improvement occurs, the dosage should be reduced gradually to the minimum maintenance level and discontinued if at all possible. Treatment should not exceed 5 days.

A course of treatment should not be repeated within 28 days unless specifically indicated and prescribed by the medical practitioner.

Paediatric population

The safety and efficacy of BETADEXAMINE TABLETS in children younger than 12 years of age have not been established.

Method of administration

For oral administration.

4.3. Contraindications

BETADEXAMINE TABLETS are contraindicated in:

- Patients who are hypersensitive to betamethasone, dexchlorpheniramine or to any of the excipients in BETADEXAMINE TABLETS (see section 6.1), or medicines of similar structures.
- Patients with systemic infections (including fungal infections).
- New-borns and premature infants.
- Patients receiving monoamine oxidase inhibitors (MAOIs).

Safety in children has not been established (see sections 4.2 and 4.4)

4.4. Special warnings and precautions for use

The use of BETADEXAMINE TABLETS may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned against driving, operating machinery or performing potentially hazardous tasks where the loss of concentration may lead to accidents.

Recent myocardial infarction

Caution is advised with the use of corticosteroids in patients who have suffered a recent myocardial infarction because of the risk of myocardial rupture.

Immunisation

While on corticosteroid therapy, such as BETADEXAMINE TABLETS, patients should not be vaccinated against smallpox. Other immunisation procedures should not be undertaken in patients receiving corticosteroids, especially those receiving high doses.

Infections

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

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 close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention.
Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased. Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

Measles

Patients 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.

Pheochromocytoma Crisis

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

HPA (hypothalamic–pituitary–adrenal)-axis

Long-term use of corticosteroids, particularly in high doses and in young children can lead to suppression of the HPA-axis. This may lead to Cushingoid signs, growth and development retardation in children and increased susceptibility to stress and adrenal crisis in all patients. Patients undergoing stress, such as major surgery, septicaemia or trauma, who have signs of HPA-axis suppression, should receive replacement therapy to prevent a possible adrenal crisis.

Corticosteroids, as contained in BETADEXAMINE TABLETS, should be used with caution in:

- Ulcerative colitis,
- active or latent peptic ulcer,
- abscess or other pyogenic infections,
- active tuberculosis,
- systemic fungal infections,
- renal failure,
- hypertension,
- osteoporosis,
- hyperthyroidism, hypothyroidism,
- cirrhosis,
- ocular herpes simplex infection,
- glaucoma,
- diverticulitis,
- fresh intestinal anastomoses,
- myasthenia gravis,

- congestive heart failure,
- patients with diabetes mellitus (or a family history of diabetes),
- elderly patients,
- existing or previous history of severe affective disorders (especially previous steroid psychosis),
- previous corticosteroid-induced myopathy,
- liver failure - blood levels of corticosteroid may be increased, (as with other medicines which are metabolised in the liver),
- epilepsy.

Psychiatric disorders

Corticosteroids, as contained in BETADEXAMINE TABLETS, may aggravate existing emotional instability or psychotic tendencies.

Eye disorders

Prolonged use of corticosteroids, as contained in BETADEXAMINE TABLETS, may produce posterior subcapsular cataracts and glaucoma and may enhance secondary ocular infections due to fungi or viruses.

Visual disturbance may be reported with systemic and topical use of corticosteroids, as contained in BETADEXAMINE TABLETS. 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.

Acetylsalicylic acid

Corticosteroids may decrease blood salicylate concentrations. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

Duration of treatment

BETADEXAMINE TABLETS contains a potent, long acting corticosteroid.

The recommended treatment period should not be exceeded (see section 4.2).

General

With corticosteroid therapy, such as BETADEXAMINE TABLETS dietary salt restriction and potassium supplementation may be considered. All corticosteroids increase calcium excretion.

Concomitant glucocorticoid therapy may inhibit the response to somatotropin.

Dexchlorpheniramine, as contained in BETADEXAMINE TABLETS, should be used in caution in patients with:

- Narrow angle glaucoma and increased ocular pressure.
- stenosing peptic ulcer,
- pyloroduodenal obstruction,
- prostatic hypertrophy or bladder neck obstruction,
- cardiovascular disease including hypertension,
- hyperthyroidism,
- renal or hepatic impairment,
- seizures.

Elderly

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

Paediatric population

Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time (see section 4.2).

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BETADEXAMINE TABLETS.

4.5. Interaction with other medicines and other forms of interaction

Betamethasone

The dosage and therapeutic effects should be monitored closely when BETADEXAMINE TABLETS are used concurrently with:

- Phenobarbitone, phenytoin, rifampicin, carbamazepine, primidone, aminoglutethimide, rifabutin or ephedrine (reduced steroid effect).
- Anti-hypertensives and diuretics are antagonised by corticosteroids such as BETADEXAMINE TABLETS.
- Oestrogen, such as contained in oral contraceptives (increased steroid effect) .
- Potassium-depleting diuretics such as thiazides, cardiac glycosides, digoxin, acetazolamide, loop diuretics, carbenoxolone, ulcer healing medicines, theophylline or amphotericin B (increased hypokalaemia).
- Warfarin (increase in PTT), close monitoring is required.
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (aggravated ulcerogenic effect).
- Antidiabetic medicines, including insulin (dosage adjustment).

- The renal clearance of salicylates is increased by corticosteroids such as BETADEXAMINE TABLETS and steroid withdrawal may result in salicylate intoxication (see section 4.4).
- Ritonavir may result in increased plasma concentrations or corticosteroids.
- The effect of corticosteroids may be reduced 3 to 4 days after mifepristone.
- Corticosteroids may antagonise the effects of neuromuscular blocking medicines such as vecuronium.
- Concurrent use of corticosteroids and fluoroquinolones may result in increased risk of tendon rupture.
- Concomitant use of betamethasone with quetiapine may result in the increased metabolism of quetiapine and, depending on the clinical response, a higher dose of quetiapine may need to be considered.
- Co-treatment with CYP3A inhibitors, including cobicistat-containing medicines, is expected to increase the risk of systemic side effects. The combination should be avoided and patients should be monitored for systemic corticosteroid side effects.
- Corticosteroids may enhance the metabolism of tretinoin resulting in decreased levels of tretinoin.

Steroids may reduce the effects of anticholinesterases in myasthenia gravis, cholecystographic X-ray media and nonsteroidal anti-inflammatory agents.

Dexchlorpheniramine maleate

Caution should be exercised when dexchlorpheniramine maleate is given concurrently with:

- Alcohol, tricyclic antidepressants, barbiturates or other central nervous system depressants (potentiation of sedative effect).
- Oral anti-coagulants (decrease in prothrombin index (PI)).

Monoamine oxidase inhibitors (MAOIs) may prolong and intensify the anticholinergic and CNS depressive effects of some antihistamines and may cause a decrease in blood pressure.

Antihistamines, as contained in BETADEXAMINE TABLETS should be discontinued approximately 48 hours prior to skin testing procedures since these medicines may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

4.6. Fertility, pregnancy and lactation

The safety of BETADEXAMINE TABLETS in pregnancy and lactation has not been established.

Pregnancy

Betamethasone as contained in BETADEXAMINE TABLETS readily crosses the placenta. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation 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 occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Myocardial hypertrophy and gastroesophageal reflux have been reported in association with *in-utero* exposure to betamethasone.

When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state. Patients with pre-eclampsia or fluid retention

require close monitoring. Betamethasone, systemically administered to a woman during pregnancy may result in a transient suppression of the foetal heart rate parameters and biophysical activities that are widely used for the assessment of foetal wellbeing. These characteristics can include a reduction in foetal breathing movements, body movements and heart rate.

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Safety during pregnancy has not been established.

Breastfeeding

Corticosteroids, as contained in BETADEXAMINE TABLETS may pass into breast milk, although no data are available for betamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

Dexchlorpheniramine is excreted in breast milk. Therefore caution should be exercised when administered to nursing mothers.

Fertility

Betamethasone, as contained in BETADEXAMINE TABLETS may alter the motility and number of spermatozoa.

4.7. Effects on ability to drive and use machines

BETADEXAMINE TABLETS has a major influence on the ability to drive and use machinery. Since adverse reactions such as drowsiness have been reported in patients receiving BETADEXAMINE TABLETS, patients should not drive, use machinery or perform any tasks that

require concentration, until they are certain that BETADEXAMINE TABLETS does not adversely affect their ability to do so (see section 4.4 and 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

Betamethasone

Adverse reactions reported after use of corticosteroids include fluid and electrolyte disturbances, musculoskeletal, gastrointestinal, dermatologic, neurologic, endocrine, ophthalmic, metabolic and psychiatric disturbances.

Dexchlorpheniramine maleate

Slight to moderate drowsiness is the most frequent side effect of dexchlorpheniramine maleate.

b) Tabulated list of adverse reactions

System organ class	Frequent	Frequency unknown (cannot be estimated from the available data)
Infections and infestations		Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs[2], opportunistic infections[2], recurrence of dormant tuberculosis[2] (see section 4.4)
Blood and the lymphatic system disorders		Haemolytic anaemia[1], hypoplastic anaemia[1], thrombocytopenia[1], agranulocytosis[1]
Immune system disorders		Anaphylactic shock[1]
Endocrine disorders		Suppression of the HPA axis[2], growth suppression in infancy[2], childhood and adolescence[2], menstrual irregularity[2], amenorrhoea[2]
Metabolism and nutrition disorders		Cushingoid facies[2], hirsutism[2], weight gain[2], impaired carbohydrate tolerance with increased requirement for antidiabetic therapy[2]*
Psychiatric disorders		A wide range of psychiatric reactions**,
		confusion[1], restlessness[1], excitation[1], nervousness[1], irritability[1], insomnia[1], euphoria[1], hysteria[1], depression[1], inability to concentrate[1], hallucinations[1], anxiety[1]
Nervous system disorders	Slight to moderate drowsiness[2]	Dizziness[1,2#], sedation[1,2#],
		headache[1], disturbed coordination[1], tremor[1], paraesthesia[1], neuritis[1], convulsions[1],

		hypereflexia[1], hyporeflexia[1], facial dyskinesias[1], seizures[1],
Eye disorders		Increased intra-ocular pressure[2], glaucoma[2], papilloedema, posterior subcapsular cataracts[2], corneal or scleral thinning[2], exacerbation of ophthalmic viral or fungal diseases[2], blurred vision[1,2] (see section 4.4),
		diplopia[1], dilated pupils[1]
Ear and labyrinth disorders		Vertigo[1], tinnitus[1], acute labyrinthitis[1]
Cardiac disorders		Myocardial rupture following recent myocardial infarction[2],
		palpitations[1], tachycardia[1], extrasystoles[1]
Vascular disorders		Hypertension[1], hypotension[2#], thrombo-embolic complications[1]
Respiratory, thoracic and mediastinal disorders		Dryness of nose, mouth and throat[2],
		Thickening of bronchial secretions[1], tightness of chest[1], wheezing[1], nasal stuffiness[1]
Gastrointestinal disorders		Abdominal distension[2], oesophageal ulceration[2], nausea[2], dyspepsia, peptic ulceration with perforation[2], haemorrhage[2], acute pancreatitis[2], candidiasis[2],
		epigastric distress[1], anorexia[1], nausea[1], vomiting[1], diarrhoea[1], constipation[1], xerostomia[1], appetite stimulation[1]
Skin and subcutaneous tissue disorders		Impaired healing[2], skin atrophy[2], bruising[2], telangiectasia[2], striae[2], acne[2], Stevens-Johnson syndrome[2],
		Urticaria[1], medicine rash[1], photosensitivity[1]
Musculoskeletal and connective tissue disorders		Muscular weakness[2]
		Osteoporosis[2], vertebral and long bone fractures[2], avascular osteonecrosis[2], tendon rupture[2], proximal myopathy[2]
Renal and urinary disorders		Urinary frequency[1], difficult urination[1], urinary hesitation and retention[1], early menses[1]
General disorders and administrative site conditions		Chills[2],
		leucocytosis[2], thrombo-embolism[2], malaise[2], hiccups[2],
		excessive perspiration[1], fatigue[1], lassitude[1]

[1] Betamethasone

[2] Dexchlorpheniramine

[#] In patients over 60 years of age.

c) *Description of selected adverse reactions*

Other possible side effects of antihistamines include cardiovascular, haematologic, neurologic, gastrointestinal, genito-urinary and respiratory reactions.

* Negative protein, nitrogen and calcium balance. Increased appetite. Hyperhidrosis. Increased high - density lipoprotein and low - density lipoprotein concentrations in the blood. Fluid and electrolyte disturbance (Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis).

** Including affective disorder (such as irritable, euphoric, depressed and labile mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to the 5 % to 6 %. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. Psychological dependence. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Betamethasone

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Dexchlorpheniramine

Antihistamine overdosage effects may vary from central nervous system depression (apnoea, dysrhythmias, cardiovascular collapse, cyanosis, diminished mental alertness, sedation) to stimulation (convulsions, hallucinations, insomnia or tremors) to death. Other signs and symptoms may be ataxia, blurred vision, dizziness, hypotension and tinnitus. Stimulation is particularly likely in children, as are atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing; gastrointestinal symptoms and hyperthermia).

Treatment

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 21.5.4 Corticosteroid combinations

Pharmacotherapeutic group: Antihistamines for systemic use, dexchlorpheniramine combinations.

ATC code: R06AB52

Mechanism of action

BETADEXAMINE TABLETS combine the anti-inflammatory and anti-allergic effects of the corticosteroid betamethasone with the antihistaminic activity of dexchlorpheniramine maleate.

5.2. Pharmacokinetic properties

Betamethasone

Absorption

Betamethasone is absorbed from the gastrointestinal tract.

Distribution

Betamethasone 0,25 mg is therapeutically equivalent to 1,6 mg of prednisone and has a pharmacological half-life of 5 to 6 hours but a biological active half-life of 36 to 72 hours. After oral administration it is 72 % bioavailable. As an anti-inflammatory it is 6 times more potent than prednisone but has less mineralocorticoid (salt retention) effect than prednisone.

Biotransformation

Synthetic corticosteroids, such as prednisolone, have increased potency when compared to the natural corticosteroids, due to their slower metabolism and lower protein-binding affinity.

Elimination

Corticosteroids are metabolised mainly in the liver but also in the kidney, and are excreted in the urine.

Dexchlorpheniramine

The absorption, distribution, metabolism and elimination of dexchlorpheniramine have not been specifically described.

Absorption

However, since dexchlorpheniramine is the primary active isomer of the racemic compound chlorpheniramine, the pharmacokinetics of dexchlorpheniramine are likely to be similar to that of chlorpheniramine. Dexchlorpheniramine is administered orally. H1-antagonists are generally well absorbed from the GI tract.

Distribution

The onset of action of immediate release formulations of chlorpheniramine is about 30 to 60 minutes. The C_{max} of chlorpheniramine occurs in about 2 hours, the maximum therapeutic effect in about 6 hours, and the duration of action lasts between 4 to 8 hours. Protein binding is approximately 72 %. Chlorpheniramine is widely distributed in body tissues and fluids, and it crosses the placenta and is excreted into breast milk.

Biotransformation

The metabolism of chlorpheniramine is extensive and rapid, first occurring in the gastric mucosa and then on first-pass through the liver, which may be saturable. N-dealkylation produces several metabolites, which are excreted in the urine along with the parent compound. The half-life in healthy adults and children is 20 to 24 hours and 10 to 13 hours, respectively. Dexchlorpheniramine has a mean half-life of 30 hours, (shorter in children) and after oral administration it is 25 % to 50 % bioavailable.

Elimination

Excretion rates are dependent on the pH of urine and urinary flow, with the rate decreasing as the pH rises and urinary flow decreases.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anhydrous lactose, corn starch, gelatin, magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

Round polypropylene tube with a polyethylene cap and desiccant stopper, in a carton. Pack size of 30 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

48/21.5.4/0075

9. DATE OF FIRST AUTHORISATION

06 April 2022

10. DATE OF REVISION OF TEXT

14 November 2023

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