1. NAME OF THE MEDICINAL PRODUCT

Betnesol tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 0.5 mg betamethasone (as sodium phosphate)

Excipient with known effect:

Each tablet contains 22 mg of sodium and 6 mg of sodium

benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Appearance: Pink, round, on both sides, tablet with beveled edges, with a breakline on one side and embossed with "BETNESOL" on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diseases responsive to oral glucocorticosteroid therapy.

4.2 Posology and method of administration

Glucocorticoids should only be administered at lowest therapeutic required doses and as long as it is absolutely necessary to achieve and maintain the desired therapeutic effect.
The dosage must be adjusted to the specific situation of the patient, considering severity of disease of the occurred effect and glucocorticoid tolerance.
Posology
Adults and adolescents *over* 12 years *of age*
The daily dose is administered usually in the morning and at once as this will less affect the rhythm of adrenal cortex-secretion.
Short-term treatment
Acute asthma attacks, pollinosis or other allergic diseases of the respiratory tract, generalised eczema, urticaria, dermatitis medicamentosa, and various inflammatory skin diseases.
6 tablets in the morning for 2 days, followed by
1 tablet in the morning for 2 days, followed by
½ tablet in the morning for 2 days.

Arthritis rheumatica:
1-4 tablets (0,5 mg to 2 mg) daily in the morning for 1-2 weeks, then a gradual withdrawal of treatment, starting with one tablet less a day, later half a tablet less, by keeping each dosage for one week. Thus it is possible to evaluate the minimum effective dose.
Other diseases:
Betnesol effervescent tablets is indicated particularly for patients with nephrosis since it shows nearly no sodium chloride and water retention effect. In this disease the usual dose is 1-8 tablets (0,5 mg to 4 mg) daily in the morning for 1 to 3 weeks, maybe also longer.

Then the medication is withdrawn step by step. To reach the therapeutic effect in pemphigus, erythematosus or collagenosis of the skin often higher doses are required.

Dosage in children *over* 6 years *of age*

The effects of glucocorticoids on the pathophysiology and history of the disease are considered similar in adults and children.

In children in general lower doses than indicated above are sufficient, but dosage should be adjusted more to the severity of the disease than to age, body weight, or body size. After sufficient response Betnesol should be withdrawn step by step as quickly as possible. Long-term treatment is not recommended. Exact dosages have not been established in clinical trials. From clinical experience following guidelines for short-time treatment were shown:
Recommended initial dose:
7 to 12 years: up to 8 tablets/day (= 4 mg).

Elderly

Caution is advised on higher frequency of adverse events in older patients during administration of betamethasone particularly in long-term therapy including osteoporosis, worsening diabetes, hypertension, susceptibility to infections and thinning of the skin.

Patients with impaired liver function and thyroid disease

Betamethasone is basically metabolized in the liver. In patients with hepatic insufficiency or hypothyroidism relatively low doses may be sufficient or dose reduction may be required.

Method of administration

Betnesol tablets should be solved in water and then the solution should be drunk, or the tablets could be swallowed whole with some water.
Only for short-term treatment

The dosage to continue therapy has to be adjusted to the disease and the response of the patient. The patient must therefore be monitored and the dosage checked frequently or adjusted, respectively.
Maintenance doses of more than 7.5 mg prednisolone equivalent/day (= Cushing threshold dose; corresponding approximately to 1 mg betamethasone) have to be avoided, because they suppress the endogenous cortisol production by hypothalamic inhibition without reaching the intended pharmacologic effects.
To lower the undesired effects the following therapy instructions have to be followed:

- lowest therapeutic required dose and shortest duration of therapy.

Although short-term high-dosage glucocorticoid administration (up to 10 days) is not critical, an initial high dose should be lowered to a maintenance dose below twice the Cushing threshold dose within short time.
The entire dose should be administered in the morning before 8 o'clock, since the rhythm of adrenal secretion.
In children and adolescents up to 14 years a 4 days-therapy-free interval (intermittent therapy) should be kept following 3-days therapy because of the risk of growth retardation.

Withdrawal has to be done solely with treatment pauses.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications for administration beyond emergency therapy:

- Systemic mycosis
- Ulcus ventriculi
- Ulcus duodeni
- Severe osteoporosis
- Myopathies (excluding Myasthenia gravis)
- Virus diseases (e.g. varicella, herpes simplex, herpes zoster – viraemic phase))
- Poliomyelitis with the exception of bulbar encephalitic form)
- Lymphadenopathyfollowing BCG – immunisation
- Approximately 8 weeks before and 2 weeks after immunization or 1 year after a BCG vaccination

- Narrow-angle glaucoma and open-angle glaucoma
- Manifest or latent tuberculosis
- Amoebic infections
- Anamnestic psychoses
- Herpes keratitis
- Children under 6 years of age

4.4 Special warnings and precautions for use

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.

Betnesol therapy should only be carried out with strict diagnostic criteria, and with additional targeted anti-infective therapy where appropriate for:

- HBsAg positive chronic active hepatitis
- Hardening of the lymph nodes (up to one year after a BCG vaccination specific histiocytosis should be excluded prior to starting therapy)
- Acute and chronic bacterial infections
- History of tuberculosis (caution: reactivation); Administration only with tuberculostatic protection

In addition Betnesol therapy should only be carried out with strict diagnostic criteria, and with additional targeted anti-infective therapy where appropriate for:

- Hypertension that is difficult to control
- Diabetes mellitus that is difficult to control
- Corneal ulcers and injuries
- Epilepsy
- Thrombophilia/thromboembolic processes
- Heart failure
- Renal failure

Because of the risk of intestinal perforation with peritonitis Betnesol may be used if there is a compelling indication and only under appropriate supervision for:

- Severe ulcerative colitis with impending perforation, abscess or purulent inflammation
- Diverticulitis
- Enteroanastomosis (immediately after surgery).

Glucocorticoids may only be used in severe infections in combination with casual therapy.
Before starting glucocorticoid therapy, a detailed investigation must be carried out; and in particular, gastric and intestinal ulcers should be excluded.
For the prevention of ulcers in the gastrointestinal tract, the administration of acid inhibitors and careful monitoring (including X-ray control/gastroscopy) is indicated in sensitive patients.
The signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoid.
Systemic glucocorticoid treatment can lead to a deterioration in carbohydrate metabolism, which can lead to the manifestation of latent diabetes or worsening of manifest diabetes.
In diabetics, the metabolic status must therefore be checked and if necessary antidiabetic treatment must be adjusted.
During treatment with Betnesol, regular blood pressure monitoring is required in patients with hypertension.
In the treatment of myasthenia gravis, the symptoms may worsen at the beginning, therefore glucocorticoid adjustment should be carried out in hospital. If irritation in the face and throat are particularly severe and respiration is impaired, treatment with Betnesol should be started gradually.
Treatment with Betnesol may mask the symptoms of existing or developing infection and

thus complicate the diagnosis.
Treatment with glucocorticoids can lead to an increased risk of infection due to immunosuppression, in particular by opportunistic germs.
Immunisation with inactivated vaccines is generally possible. It should be noted however that the immune response and hence success of the vaccination could be impaired at higher corticosteroid doses.
At high doses, it is important to ensure an adequate intake of potassium and sodium restriction. Serum potassium levels should be monitored and adapted if necessary. This especially applies to simultaneous administration of medicines which are known to cause QT interval extension.
Certain viral diseases (chickenpox, measles, Herpes zoster) can be more severe in patients who are treated with glucocorticoids. Immunocompromised children and persons who have not been previously infected with chickenpox or measles are at risk. If these patients come in contact with infected persons during treatment with Betnesol, preventive therapy should be initiated if necessary.
Due to the growth-inhibiting effect of glucocorticoids, they should only be used in children if there are compelling medical reasons and height growth should be monitored regularly.
If physical stress (e.g. accident, surgery, birth) occurs during treatment with glucocorticoids a temporary dose increase may be necessary. Due to the possible danger in stressful situations, a corticosteroid identity card should be issued for patients on long-term treatment.
Depending on duration and dose of the treatment, a negative effect on calcium metabolism must be taken into account, and osteoporosis prevention recommended if necessary.
Prevention consists of adequate calcium and vitamin D intake and physical activity. For existing osteoporosis, additional medical treatment should be considered.
Relatively low doses may be sufficient for patients with hypothyroidism or liver cirrhosis and a general dose reduction may be necessary.
Betnesol is primarily intended for short-term use. If used for a longer period of time, warnings such as those described for glucocorticoid-containing drugs for long term use, must also be observed.
At the end or required discontinuation of long-term systemic treatment with glucocorticoids caution is advised to avoid acute adrenal insufficiency (especially under stress, such as infections, accidents, increased physical stress, and fever), withdrawal syndrome or a relapse of the disease.

Too rapid dose reduction after long-term treatment may lead to symptoms such as

muscle and joint pain.
Patients should be advised to inform subsequent physicians (e.g. surgery, travel, vaccinations) of the treatment with corticosteroids.
In long-term glucocorticoid therapy, independent of disease-related checks, and depending on the dosage and the individual condition of the patient, monitoring at reasonable intervals, for possible undesirable events may be necessary.

Visual disturbance
Visual disturbance can occur 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.
Athletes
Administration of Betnesol tablets can lead to a positive doping test result.

This medicine contains:
less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free"
- 6 mg sodium benzoate in each tablet. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in new-born babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

Heart glycosides	Increased glycoside action by hypokalaemia
Medicinal products leading to QT prolongation	Hypokalaemia has to be corrected if appropriate and clinical condition has to be
Antidiabetics	The blood glucose-lowering effect of insulin and oral antidiabetics can be reduced.
Cumarin derivates	Action of anticoagulants is decreased
Anticoagulants	Possible increased or decreased anti-coagulant
Barbiturates, Hydantoin, Rifampicin	Action of corticoids is decreased
Nonsteroidal antiphlogistics, antirheumatics	Increased incidence of stomach ulcers and stomach bleeding
Oestrogens	Corticoid action may be increased, therefore dose adjustment may be necessary if oestrogens are used or discontinued.
Vaccines	Live vaccines may be more toxic due to the immune suppressing effect of corticosteroids Disseminated viral infections can occur. For inactivated or toxoid vaccines the immune response can fail or can be reduced (see 4.3 Contraindications)
Aluminium salts - complex-forming acids	If taken in combination with complex-forming acids, such as citric acid in drinks or medicinal products (for the treatment of acidosis or urinary alkalinisation) or ascorbic acid for several weeks, the aluminium concentration in the plasma may increase.
Bupropion	Increased risk of seizures.
Quinidine	The action of quinidine may be increased.
Non-depolarising muscle relaxants	Muscle relaxation may last longer.
Atropine, other anticholinergics	Possible additional increase of intraocular
Praziquantel	Possible decrease of the concentration of praziquantel in the
Chloroquine, Hydrochloroquine, Mefloquine	Increased risk of myopathy and
Somatropin	Effect of somatropin may be reduced
Protirelin	After administration of protirelin, TSH increase
Ciclosporin	Possible increase of cyclosporine blood levels. Increased risk of cerebral
ACE-Inhibitors	Increased risk of blood count changes.
Ephedrine	The metabolism of glucocorticoids can be accelerated and this can reduce its efficacy.
Diuretics	Increased loss of potassium - increased risk of hypokalaemia.
Azole Antimycotics (such as ketoconazole or itraconazole)	Increased action of glucocorticoids
Enzyme inductors (CYP 3A4)	Decreased action of glucocorticoids
Copper (intrauterine devices)	Decreased action of intrauterine devices
Lithium salts	Possible decreased action of lithium
Influence on analytical methods	Skin reactions to allergy tests (prick test) may be suppressed.
CYP3-inhibitors (including cobicistat-containing products)	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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no controlled studies on the administration of betamethasone during pregnancy and lactation available.

In animal studies the use of glucocorticoids led to foetal malformations (see section 5.3). An increased risk of cleft palate in human foetus by the administration of glucocorticoids during the first trimester is under discussion. If glucocorticoids are administered at the end of pregnancy, there is a risk for the foetus of atrophy of the adrenal cortex, and substitution treatment of the new-born may be required. Furthermore, they will also need to be tested for the rare occurrence of congenital cataracts.

For this reason, Betnesol should only be administered during pregnancy if the expected benefit outweighs the potential risk for the foetus.

Generally speaking, no cortisone-containing medicinal products should be administered in the first 3 months of pregnancy.

Breastfeeding

Since glucocorticoids penetrate breast milk in small quantities, breastfeeding should be stopped during glucocorticoid treatment.

Fertility

No data are available on effects on fertility

4.7 Effects on ability to drive and use machines

No studies have been carried out on the effects of the ability to drive and to use machines. However, based on the known pharmacodynamics and pharmacokinetic of the active ingredient it can be assumed that Betnesol has no direct influence on the ability to drive and the ability to operate machines. Some adverse events during cortisone therapy (eye disorders, nervous system disorders or myopathy) may reduce the ability to drive.

4.8 Undesirable effects

The frequencies of undesirable effects are ranked according to the following:

Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000, <1/1,000)
Very rare
(<1/10,000)
Not known (frequency cannot be estimated from the available data)

Table 1: Undesirable effects that occurred with

systemic betamethasone

System organ classes and	Undesirable effects
Endocrine disorders	
Not known	Cushing's syndrome, inactivation or atrophy of the adrenal cortex
Gastrointestinal disorders	
Not known	Abdominal discomfort, Ulcus ventriculi or duodeni (risk of perforation), ulcerative oesophagitis, bleeding, pancreatitis; risk of perforation with pre-existing Colitis ulcerosa
Infections and infestations	

Not known	Increased risk of susceptibility to infections; masking of infections; exacerbation of latent infections (mycosis, virus infections, bacterial infections, protozoa infection, candidosis,
Blood and lymphatic system disorders	
Not known	Leucocytosis.
Immune system disorders	
Not known	Decreased immune response; allergic reaction, anaphylactic reactions including shock.
Eye disorders	
Not known	Cataract, glaucoma, exophthalmos, blurred vision (see also section
Cardiac disorders	
Not known	Myocardial rupture after recent infarct
Metabolism and nutritional disorders	
Not known	decreased carbohydrate tolerance, diabetes mellitus, oedema, osteoporosis, sodium retention with formation of oedema, increased potassium excretion, catabolic effect on protein metabolism (negative nitrogen balance),
Musculoskeletal and connective tissue and bone disorders	
Not known	Muscle atrophy and weakness, myopathy, growth retardation in children, osteoporosis, osteonecrosis (Femur and Capitulum humeri), tendon rupture
Psychiatric disorders	
Not known	Mental disorders, psychosis, personality changes, confusion.
Nervous system disorders	
Not known	Insomnia, vertigo, headache, Pseudotumor cerebri (particularly in children), manifestation of latent epilepsy und increase of seizures in manifest epilepsy, increased nervousness and
Reproductive system and breast disorders	
Not known	Disturbance of sexual hormone secretion (menstrual disorders,
Skin and subcutaneous tissue disorders	
Not known	Striae rubrae, atrophy, telangiec tasia,
Vascular disorders	
Not known	Hypertension, thrombosis, vasculitis
Respiratory, thoracic and mediastinal disorders	
Not known	Hiccups

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

In acute overdose with glucocorticoids including betamethasone, a life-threatening situation is not to be expected. Also at extremely high doses, excessive doses of glucocorticoid over several days will not lead to any risk for the patient, if special contraindications such as diabetes, glaucoma, gastrointestinal ulcers. as well as concomitant treatment with potassium sparing diuretics, digitalis, anticoagulants (coumarin type) can be excluded.

Any undesirable events due to glucocorticoids that occur, must be treated symptomatically accordingly. For ulcer prophylaxis, a H2 receptor antagonist or antacid should be administered. In diabetics blood glucose levels must be monitored and antidiabetic drugs dose should be increased if necessary. At increased risk of infection antibiotic treatment may be necessary.

Treatment: Symptomatic; Adequate hydration. Control of electrolytes in serum and urine, in particular the balance of sodium and potassium. Disturbed electrolyte imbalance should be compensated.

There is no known antidote for betamethasone.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, pure, glucocorticoids, betamethasone
ATC Code: H02AB01
Betamethasone is a mono-fluorinated glucocorticoid, which has an approximately 25-fold more potent anti-inflammatory effect than the natural adrenal hormone cortisol. The mineralocorticoid effect-component is however almost completely absent.
Glucocorticoids such as betamethasone develop their biological effect by activating the transcription of corticosteroid-sensitive genes. The anti-inflammatory, immunosuppressive and antiproliferative effects are caused for example by reduced formation, release and activity of inflammatory mediators and by inhibition of specific functions and migration of inflammatory cells. In addition, corticosteroids may prevent the effect of sensitised T-lymphocytes and macrophages on target cells.
Glucocorticoids such as betamethasone promote surfactant synthesis in the foetal lung.
Possible induction of temporary adrenal insufficiency must be taken into account with necessary long-term corticosteroid medication. Suppression of the hypothalamus-pituitary-adrenal axis also depends on individual factors.
The Cushing's threshold dose is specified at 1.5 mg / day.
Betamethasone is a glucocorticoid which is 8 to 10 times more active than prednisolone (based on weight; 750µg betamethasone corresponding to approximately 5 mg prednisolone). Betamethasone sodium phosphate is highly soluble in water and is therefore quickly absorbed. Betamethasone usually only causes poor retention of sodium chloride or water. Due to lack of mineralocorticoid properties betamethasone is particularly suitable for the treatment of diseases where water retention is adversely affected.

5.2 Pharmacokinetic properties

Betamethasone sodium phosphate is hydrolysed in the body to the biologically active form betamethasone, reaches the highest blood levels within 60 minutes and is excreted almost entirely after the first day.

Corticosteroids are in general absorbed liberally in the gastrointestinal tract, bound to plasma proteins in varying degrees, primarily metabolised in the liver and excreted by the kidneys.
Corticosteroids are rapidly distributed in all body tissues. They cross the placenta to varying degrees and small quantities may be distributed into breast milk. The (serum) elimination half-life of betamethasone in adults is approximately 5-7 hours.
Betamethasone has a protein binding of 62.5% (compared to hydrocortisone 89%).
While the plasma half-life of betamethasone is ≥300 minutes, the biological half-life was identified as 36-54 hours. Due to the long duration of action, betamethasone hence may lead, with daily continuous administration, to continuous accumulation and overdose. In patients with liver disease degradation is slower.
When betamethasone sodium phosphate was used infiltratively in healthy volunteers, a negative feedback mechanism on the hypothalamic-pituitary system lead to suppression of the cortisol plasma level within approximately 8-10 hours. This was normalised within a few days.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, non-clinical data reveal no special hazard for humans other than those known for corticosteroids, repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproductive toxicity

Following parenteral administration Betamethasone showed teratogenic effects in rats and rabbits.

The most common malformations were cleft palates. Higher doses showed embryonic lethality. Animal studies showed evidence of malformations and other embryo-toxic effects. During long-term therapy intrauterine growth retardation cannot be excluded. With administration at the end of pregnancy the foetus is at risk of atrophy of the adrenal cortex (see 4.6).

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acid citrate, sodium bicarbonate, sodium benzoate, Povidone 30, saccharin-sodium, Erythrosine (E127).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

Store in the original package to protect the content from light.

6.5 Nature and contents of container

LDPE/Alu blister pack

Betnesol tablets are available with 10 and 30 packs.

6.6 Special precautions for disposal and other handling

No special requirements

7. MANUFACTURER

Alfasigma S.p.A., Via Ragazzi del ’99, n.5, Bologna, Italy

8. LICENSE HOLDER

Devries & Co.
32 Habarzel st.
Tel-Aviv

9. MARKETING AUTHORISATION NUMBER

135 65 22066 00

10. DATE OF REVISION OF THE TEXT

Revised in January 2022 according to MOH guidelines.