SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG

BENTELAN 0.5 mg effervescent tablets
BENTELAN 1 mg effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BENTELAN 0.5 mg effervescent tablets
One 0.5 mg tablet contains:
Betamethasone disodium phosphate 0.6578 mg
equal to Betamethasone 0.5 mg
Excipient with known effects: Sodium 20,4 mg

BENTELAN 1 mg effervescent tablets
One 1 mg tablet contains:
Betamethasone disodium phosphate 1.316 mg
equal to Betamethasone 1 mg
Excipient with known effects: Sodium 19.6 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid treatment can be indicated in a wide range of diseases.
The main diseases include:
- bronchial asthma
- severe allergic diseases
- rheumatoid arthritis
- collagenopathy
- inflammatory dermatoses
- neoplasms, especially of lymphatic tissue (acute and chronic malignant haemolymphopathy, Hodgkin's disease).

Other indications are: nephrotic syndrome, ulcerative colitis, segmental ileitis (Crohn's disease), pemphigus, sarcoidosis (especially hypercalcemic), rheumatic carditis, ankylosing spondylitis and various dyscrasic haemopathies, such as certain cases of haemolytic anaemia, agranulocytosis and thrombocytopenic purpura.

4.2 Dosage and method of administration

Dosage
Adults:
Short-term treatments:
4-6 tablets per day of BENTELAN 0.5 mg effervescent tablets or 2-3 tablets per day of BENTELAN 1 mg effervescent tablets (equivalent to 2-3 mg), gradually reducing this dose according to the clinical evolution.
Long-term treatments:
In the treatment of chronic or subacute morbid forms (collagenopathies, haemolytic anaemias, chronic bronchial asthma, nephrotic syndrome, ulcerative colitis, pemphigus), after an attack treatment generally of 6-8 tablets a day of BENTELAN 0.5 mg effervescent tablets or 2-3 tablets per day of BENTELAN 1 mg effervescent tablets (equivalent to 3-4 mg), gradually reduce the dosage until reaching the minimum maintenance dose capable of keeping the symptoms under control.
Maintenance:
The maintenance dose fluctuates in the adult of average weight from between 1-2 tablets per day.

Paediatric population:
Children generally tolerate doses proportionally higher than those established for adults: 0.1-0.2 mg/Kg of body weight per day is recommended.
BENTELAN tablets can be divided in half to facilitate dosage adjustment, furthermore solubility in water allows practical and easy administration.

Aerosol therapy: 0.5-1 mg dissolved at the time of use in 1-2 ml of water.

4.3 Contraindications

Hypersensitivity to the active ingredient, to corticosteroids or any of the excipients listed in section 6.1.
Systemic infections, if no specific anti-infective treatment is implemented.
Immunization with attenuated viruses; other immunization procedures should not be undertaken in patients receiving glucocorticoids, especially at high doses, due to the possible risks of neurological complications and insufficient antibody response.

4.4 Special warnings and precautions for use

The product must be used under the personal supervision of the medical doctor.

Susceptibility to infections:
Glucocorticoids may mask some signs of infection and during their use intercurrent infections may occur due to reduced immune defences. In these cases the opportunity to establish an adequate antibiotic therapy should always be evaluated.
Patients treated with immunosuppressive doses of corticosteroids must be warned to avoid exposure to chickenpox and measles and, if exposed, to seek medical advice. This is of particular importance in children.
Use in active tuberculosis should be limited to cases of fulminant or disseminated disease, in which the glucocorticoid should be used with appropriate anti-tuberculosis treatment.
If glucocorticoids are administered to patients with latent tuberculosis or positive tuberculin disease, close monitoring is necessary because a reactivation of the disease may occur.
In prolonged treatment these subjects must receive chemoprophylaxis.

Alterations of the electrolyte balance:

Since mineralocorticoid secretion may be compromised, sodium chloride and/or mineralocorticoid should be co-administered.
Due to the possibility of fluid retention, caution should be exercised in the administration of corticosteroids to patients with congestive heart failure.
During prolonged treatment and with high doses, if an alteration of the electrolyte balance should occur, it is advisable to adjust the sodium and potassium intake.
All glucocorticoids increase calcium excretion.

Stress conditions:
In patients receiving glucocorticoid treatment who are undergoing particular stress, dose adjustment is essential in relation to the extent of the stressful condition.

In patients receiving glucocorticoid treatment who are undergoing particular stress, dose adjustment is essential in relation to the extent of the stressful condition.
Effects on the psyche: During treatment, psychic alterations of various kinds can occur: euphoria, insomnia, changes in mood or personality, severe depression or symptoms of real psychosis.
Pre-existing emotional instability or psychotic tendencies may be exacerbated by the glucocorticoid.

Paediatric population:
Children and adolescents undergoing prolonged therapy must be closely supervised from the point of view of growth and development.
Treatment should be limited to the minimum doses and to the shortest period of time possible. In order to minimize the suppression of the hypothalamic-pituitary-adrenal axis and growth delays, the possibility of carrying out a single administration every other day should be considered.
Children are particularly at risk of increased intracranial pressure.

Elderly patients:
In elderly patients, the therapy, in particular if prolonged, must be planned in consideration of the higher incidence of side effects such as osteoporosis, worsening of diabetes, hypertension, increased susceptibility to infections, and cutaneous diarrhoea.
The maintenance dosage must always be the minimum that can control the symptomatology; a dosage reduction should be done gradually over a period of a few weeks or months in relation to the dose previously taken and the duration of therapy.

Other populations at risk:
Glucocorticoids should be administered with caution in the following cases because they may induce worsening: epilepsy, diabetes mellitus, glaucoma, non-specific ulcerative colitis with danger of perforation, abscesses and pyogenic infections in general, diverticulitis, recent intestinal anastomosis, active or latent peptic ulceration, renal failure, hypertension (in predisposed patients due to changes in the electrolyte balance), osteoporosis and myasthenia gravis.
The same attention should be paid to cases of previous steroid-induced myopathy.

In patients with hepatic impairment, the blood levels of corticosteroids can be increased, as is the case with other drugs that are metabolized in the liver.
In hypothyroid patients or patients with liver cirrhosis, the response to glucocorticoids may be increased.
Caution is advised in patients with ocular herpes simplex, because corneal perforation is possible.
In patients with hypoprothrombinemia, caution is advised in combining acetylsalicylic acid with glucocorticoids.

Suspension of corticosteroid therapy
Secondary adrenal insufficiency induced by glucocorticoids can be minimized through a gradual reduction of the dose. By suspending corticosteroid therapy, the amplitude and rate of dose reduction should be determined on a case-by-case basis taking into consideration the underlying condition being treated and individual patient factors, such as the likelihood of recurrence and the duration of treatment with corticosteroids.

This type of relative insufficiency can last up to a year following the discontinuation of therapy. Therefore, in the event of any stressful conditions during this period, hormone therapy must be resumed.

Systemic effects with inhaled corticosteroids:
Systemic effects may occur with inhaled corticosteroids, particularly when prescribed at high doses for prolonged periods. These effects are less likely to occur compared to treatment with oral corticosteroids. Possible systemic effects include Cushing's syndrome, cushingoid aspect, adrenal suppression, growth retardation in children and adolescents, reduction of bone mineral density, cataracts, glaucoma and, more rarely, a series of psychological or behavioural effects that include psychomotor hyperactivity, sleep disorders, anxiety, and depression or aggression (particularly in children). It is therefore important that the dose of inhaled corticosteroid is the lowest possible dose with which effective control of asthma is maintained.

BENTELAN 0.5 mg and 1 mg effervescent tablets contain sodium, 0.89 mmol (or 20.4 mg) and 0.85 mmol (or 19.6 mg), respectively, per tablet.
This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet, meaning that it is practically 'sodium-free'.

For those who participate in sports
Use of the drug without therapeutic necessity constitutes doping and can in any case determine positive findings in anti-doping tests.

4.5 Interactions with other medicines and other forms of interaction

Steroids may reduce the effects of anticholinesterases in myasthenia gravis, radiographic contrast agents in cholecystography, salicylates and non-steroidal anti-inflammatory drugs.
Concomitant use of corticosteroids with diuretics that induce potassium depletion (such as thiazides and furosemide) may cause excessive potassium loss.
There is also an increased risk of hypokalemia with concomitant use of corticosteroids and amphotericin or xanthines (theophylline).
Steroids can also decrease the effects of salicylates, anti-diabetic drugs and insulin.
There may be an increased incidence of gastrointestinal haemorrhages and ulcers when corticosteroids are administered with non-steroidal anti-inflammatory drugs.
The concomitant use of corticosteroids and cyclosporine increases the plasma concentration of both drugs.
The effect of the steroids may be increased by the concomitant use of ritonavir and ketoconazole.
In patients with hypoprothrombinemia, caution is advised in combining acetylsalic acid with glucocorticoids.
The effect of steroids can be reduced by phenytoin, phenobarbitone, ephedrine and rifampicin.
Modification, usually decreasing, of the dosage of anticoagulants administered concomitantly may be necessary.

4.6 Pregnancy and lactation

Before prescribing systemic corticosteroids during pregnancy and lactation, the benefits of the treatment should be weighed against the potential risks for the mother and baby.

Pregnancy

In pregnant women the product should be administered in cases of actual need, under the direct supervision of the medical doctor.

Early animal studies have shown increased palatoschisis in the foetus after maternal intake of high doses of corticosteroids.

A review of the safety data of systemic corticosteroids used during pregnancy and lactation conducted by the Committee on Safety of Drugs in the UK concluded that there was no convincing evidence that corticosteroids caused an increased incidence of congenital anomalies. Prolonged or repeated use during pregnancy increased the risk of intra-uterine growth retardation, but this does not appear to be a risk in short-term treatment. It has also been observed that corticosteroids vary in their ability to cross the placenta; betamethasone and dexamethasone rapidly cross the placenta, while 88% of prednisolone is inactivated while crossing the placenta.

Lactation

The need for breastfeeding by patients treated with high doses of corticosteroids should be assessed as corticosteroids are excreted in human milk.

4.7 Effects on the ability to drive vehicles and use machinery

There is no known direct influence of the drug on the ability to drive and operate machinery that may, nevertheless, be reduced in rare cases of neurological side effects.

4.8 Undesirable effects

The frequency of undesirable effects is determined as follows:

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 determined based on the available data).

The following adverse reactions have been reported in the literature (clinical cases) or voluntarily and spontaneously reported by a population whose exact exposure rate is not known.

Since it is not possible to estimate the true frequency of adverse reactions resulting from exposure to betamethasone, their incidence has been reported as "not known".

Adverse reactions are listed below using the MedDRA system and organ classification and listed in descending order of severity.

During treatment with corticosteroids, particularly for intensive and long-term treatments, some of the following side effects may appear:

Classification by system organ class	**Adverse reactions**
Cardiac diseases	
Not known	Congestive heart failure*
Endocrine disorders	

Not known	Adrenal suppression, Adrenal atrophy, Hyperadrenocorticism, Cushing's syndrome, Diabetes mellitus, Hyperglycaemia, Hirsutism
Eye diseases	
Not known	Glaucoma, Subcapsular cataract, hypertonicity
Gastrointestinal disorders	
Not known	Gastric ulcer with perforation**, Peptic ulcer, Acute pancreatitis, Oesophagitis, Nausea
General disorders and administration site conditions	
Not known	Incomplete healing
Immune system disorders	
Not known	Anaphylactic reaction, Urticaria, Allergic dermatitis
Infections and infestations	
Not known	Tuberculosis***, Mycosis, Viral infection
Diagnostic tests	
Not known	Decreased blood potassium, Negative nitrogen balance, Decreased total protein, Decreased lymphocyte count, Reduced glucose tolerance, Increased weight, Decreased weight
Metabolism and nutrition pathologies	
Not known	Osteoporosis, Oedema, Increased appetite
Musculoskeletal and connective tissue disorders	
Not known	Osteonecrosis, Growth retardation, Myopathy, Collagen disease, Fracture, Tendon rupture
Nervous system disorders	
Not known	Increased intracranial pressure, Papilledema, Benign intracranial hypertension, Vertigo, Headache
Psychiatric disorders	
Not known	Psychotic disorder, Anxiety, Irritability
Reproductive system and breast disorders	
Not known	Menstrual disorder
Skin and subcutaneous tissue disorders	
Not known	Skin atrophy, Acne, Ecchymosis, Erythema, Hyperhidrosis, Skin changes such as delays in scarring processes
Vascular disorders	
Not known	Hypertension****

* due to the possibility of fluid retention (see section 4.4)
** in patients with pre-existing gastro-duodenal ulcer (see section 4.4)
*** reactivation (see section 4.4)

**** in patients predisposed due to changes in the electrolyte balance (see section 4.4)

Reporting of suspected adverse reactions
The reporting of suspected adverse reactions that arise after the authorization of the medicinal product is important, as it allows continuous monitoring of the benefit/risk ratio of the medicine. Healthcare professionals are asked to report any suspected adverse reaction through the Italian national reporting system at website http://www.agenziafarmaco.gov.it/it/responsabili.

4.9 Overdose

Overdose of glucocorticoids, including betamethasone, does not lead to life-threatening situations. Except for extreme dosages, an overdose of glucocorticoids for a few days is unlikely to produce dangerous results in the absence of specific clinical conditions (see section 4.4) such as diabetes mellitus, glaucoma or active peptic ulcer or concomitant treatment (see section 4.5) with digitalis, coumarin or diuretic-type drugs that cause potassium depletion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic corticosteroids: Glucocorticoids ATC Code: H02AB01

Betamethasone is a synthetic corticosteroid with an intense anti-inflammatory and anti-reactive activity, equal to around 8-10 times that of Prednisolone weight by weight.
It has little tendency to provoke the characteristic side effects of corticosteroids.
It has no appreciable mineralocorticoid activity and can not therefore be used alone in the treatment of adrenal insufficiency.

5.2 Pharmacokinetic properties

After oral administration, blood concentrations are detected in humans after 20 minutes, the blood peak occurs after 2 hours, the concentration decreases gradually over 24 hours.
The plasma half-life after both oral and parenteral administration is ≥ 300 minutes.
Betamethasone is metabolized in the liver, patients with live disease have a slower drug clearance than healthy subjects.

Protein binding is high, mainly with albumin.
Betamethasone disodium phosphate is extremely soluble; the effervescent excipients present in the BENTELAN tablet ensure its complete and rapid dissolution in water before administration, which results in:

- rapidity of absorption and therefore of action
- homogenous distribution of the active substance on a large surface of the gastric mucosa and ultimately less gastric irritation compared to other poorly soluble corticosteroids
- practicality of administration especially in children and seriously ill patients

5.3 Preclinical safety data

DL_{50} in the mouse was found to be 1460 mg/kg, oral doses of up to 1 mg/kg that resulted in lymphopenia, eosinopenia and neutrophilia were administered in the rat for 9 months.
Studies of chronic toxicity in the dog pointed to the suppressive effect on the cyclicity of the oestrus.

In rats, in both sexes, fertility reduction was observed after oral administration. At therapeutic doses, parenterally, it was found to be teratogenic in the rabbit and in the rat, while at four to eight times the therapeutic dose it caused the death of the embryos.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BENTELAN 0.5 mg effervescent tablets:
Sodium citrate, sodium bicarbonate, sodium saccharin, polyvinylpyrrolidone, sodium benzoate.

BENTELAN 1 mg effervescent tablets:
Sodium citrate, sodium bicarbonate, polyvinylpyrrolidone, sodium benzoate.

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect the product from humidity.

6.5 Nature and contents of container

Heat-sealed aluminium strips internally coated with low-density polyethylene.

BENTELAN 0.5 mg effervescent tablets – 10 tablets
BENTELAN 1 mg effervescent tablets – 10 tablets

It is possible that not all packs will be placed on the market.

6.6 Special precautions for disposal

No special instructions.

7. MARKETING AUTHORIZATION (AIC) HOLDER

Alfasigma S.p.A. - Viale Sarca, n. 223 - 20126 Milano (MI)

8. MARKETING AUTHORIZATION (AIC) NUMBER(S)

BENTELAN 0.5 mg effervescent tablets – 10 tablets - AIC. no. 019655012
BENTELAN 1 mg effervescent tablets – 10 tablets AIC no.019655051

9. DATE OF FIRST AUTHORIZATION/AUTHORIZATION RENEWAL

Date of first authorization: 6 February 1962
Date of latest renewal: June 2010

10. DATE OF REVISION OF THE TEXT

August 2017

ST 114