SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flixotide 50 micrograms Evohaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flixotide 50 micrograms Evohaler is a pressurised inhalation, suspension, delivering 50 micrograms of fluticasone propionate per actuation.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension

Flixotide 50 micrograms Evohaler does not contain any chlorofluorocarbons (CFCs).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluticasone propionate given by inhalation offers prophylactic treatment for asthma.

Adults:
Mild asthma: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular daily basis.

Moderate asthma: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone.

Severe asthma: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms. On introduction of inhaled fluticasone propionate many of these patients may be able to reduce significantly or to eliminate their requirement for oral corticosteroids.

Children: Any child who requires prophylactic medication, including patients not controlled on currently available prophylactic medication

4.2 Posology and method of administration

Patients should be made aware of the prophylactic nature of therapy with inhaled fluticasone propionate and that it should be taken regularly even when they are asymptomatic.

If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought.

Flixotide Evohaler is for oral inhalation use only. Flixotide Evohaler may be used with a Volumatic spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath.

The onset of therapeutic effect is within 4 to 7 days.

Adults and children over 16 years: 100 to 1,000 micrograms twice daily, usually as two twice daily inhalations.

Prescribers should be aware that fluticasone propionate is as effective as other inhaled steroids approximately at half the microgram daily dose. For example, a 100mcg of fluticasone propionate is approximately equivalent to 200 mcg dose of beclometasone dipropionate (CFC containing) or budesonide.

Due to the risk of systemic effects, doses above 500 micrograms twice daily should be prescribed only for adult patients with severe asthma where additional clinical benefit is expected, demonstrated by either an improvement in pulmonary function and/or symptom control, or by a reduction in oral corticosteroid therapy (see sections 4.4 and 4.8).

Patients should be given a starting dose of inhaled fluticasone propionate which is appropriate to the severity of their disease.

The dose may be increased until control is achieved or reduced to the minimum effective dose, according to the individual response.

Typical Adult Starting Doses:

For patients with mild asthma, a typical starting dose is 100 micrograms twice daily. In moderate and more severe asthma, starting doses may need to be 250 to 500 micrograms twice daily. Where additional clinical benefit is expected, doses of up to 1000 micrograms twice daily may be used. Initiation of such doses should be prescribed only by a specialist in the management of asthma (such as a consultant physician or general practitioner with appropriate experience).

The dose should be titrated down to the lowest dose at which effective control of asthma is maintained.

Typical starting doses for children over 4 years of age:

50 to 100 micrograms twice daily.

Many children's asthma will be well controlled using the 50 to 100 microgram twice daily dosing regime. For those patients whose asthma is not sufficiently controlled, additional benefit may be obtained by increasing the dose up to 200 micrograms twice daily. **The maximum licensed dose in children is 200 micrograms twice daily.**

The starting dose should be appropriate to the severity of the disease.

The dose should be titrated down to the lowest dose at which effective control of asthma is maintained.

Should this particular Flixotide presentation not offer the exact paediatric dose prescribed by the physician, please see data sheets of alternative Flixotide presentation (Accuhaler, Nebules).

Administration of doses above 1000 micrograms (500 micrograms twice daily) should be via a spacer device to help reduce side-effects in the mouth and throat (see section 4.4).

Special patient groups:

There is no need to adjust the dose in elderly patients or those with hepatic or renal impairment.

4.3. Contra-indications

Hypersensitivity to any ingredient of the preparation.

4.4 Special warnings and precautions for use

The management of asthma should follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Patients' inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inspiration to ensure optimum delivery to the lungs. During inhalation, the patient should preferably sit or stand. The inhaler has been designed for use in a vertical position.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid

dosage. In patients considered at risk, daily peak flow monitoring may be instituted.

Flixotide Evohaler is not designed to relieve acute symptoms for which an inhaled short-acting bronchodilator is required. Patients should be advised to have such rescue medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Increasing use of short-acting inhaled β_2-agonists to relieve symptoms indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective, or they need more inhalations than usual, medical attention must be sought. In this situation patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids). Severe exacerbations of asthma must be treated in the normal way.

There have been very rare reports of increases in blood glucose levels, in patients with or without a history of diabetes mellitus (see section 4.8). This should be considered in particular when prescribing to patients with a history of diabetes mellitus.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. Flixotide Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important therefore that the dose of inhaled corticosteroid is reviewed regularly and reduced to the lowest dose at which effective control of asthma is maintained.

Prolonged treatment with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children aged < 16 years taking higher than licensed doses of fluticasone (typically ≥1000mcg/day) may be at particular risk. Situations, which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

Administration of high doses, above 1000 mcg daily is recommended through a spacer to reduce side effects in the mouth and throat. However, as systemic absorption is largely through the lungs, the use of a spacer plus metered dose inhaler may increase drug delivery to the lungs. It should be noted that this could potentially lead to an increase in the risk of systemic adverse effects. A lower dose may be required. (See section 4.2).

The benefits of inhaled fluticasone propionate should minimise the need for oral steroids. However, patients transferred from oral steroids, remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate. The possibility of adverse effects may persist for some time. These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled fluticasone propionate and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see section 4.5).

Treatment with Flixotide Evohaler should not be stopped abruptly.

For the transfer of patients being treated with oral corticosteroids: The transfer of oral steroid-dependent patients to Flixotide Evohaler and their

subsequent management needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

Patients who have been treated with systemic steroids for long periods of time or at a high dose may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

After approximately a week, gradual withdrawal of the systemic steroid is commenced. Decrements in dosages should be appropriate to the level of maintenance systemic steroid, and introduced at not less than weekly intervals. For maintenance doses of prednisolone (or equivalent) of 10 mg daily or less, the decrements in dose should not be greater than 1mg per day, at not less than weekly intervals. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to employ cautiously, larger decrements in dose at weekly intervals.

Some patients feel unwell in a non-specific way during the withdrawal phase despite maintenance or even improvement of the respiratory function. They should be encouraged to persevere with inhaled fluticasone propionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors (see section 4.5).

Visual disturbance

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

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

In a small study using inhaled fluticasone propionate in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

Co-treatment with other potent CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. Other inhibitors of CYP3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Combinations should be avoided unless the benefit outweighs the potential 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

Fertility

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate on male or female fertility.

Pregnancy

There are limited data in pregnant women. Administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. It is important, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained. Treatment with fluticasone propionate should not be stopped abruptly.

Results from a retrospective epidemiological study did not find an increased risk of major congenital malformations following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (see section 5.1).

Reproductive studies in animals have shown only those effects characteristic of glucocorticosteroids at systemic exposures in excess of those seen at the recommended inhaled therapeutic dose. There is inadequate evidence of safety of fluticasone propionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Because Flixotide Evohaler delivers fluticasone propionate directly to the lungs by the inhaled route it avoids the high level of exposure that occurs when corticosteroids are given by systemic routes. Administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus (see section 5.3).

Breast-feeding
The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following inhaled application of fluticasone propionate at recommended doses are likely to be low.

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

Fluticasone propionate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000) including isolated reports and not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	Very Common
	Pneumonia (in COPD patients)	Common

	Oesophageal candidiasis	Rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations: Cutaneous hypersensitivity reactions Angioedema (mainly facial and oropharyngeal oedema), Respiratory symptoms (dyspnoea and/or bronchospasm) Anaphylactic reactions	 Uncommon Very Rare Very Rare Very Rare
Eye disorders	Vision, blurred	Not known
Endocrine Disorders	Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density cataract, glaucoma	Very Rare
Metabolism & Nutrition Disorders	Hyperglycaemia (see section 4.4)	Very Rare
Psychiatric Disorders	Anxiety, sleep disorders, behavioural changes, including hyperactivity and irritability (predominantly in children) Depression, aggression (predominantly in children)	Very Rare Not known
Respiratory, Thoracic & Mediastinal Disorders	Hoarseness/dysphonia Paradoxical bronchospasm Epistaxis	Common Very Rare Not known
Gastrointestinal Disorders	Dyspepsia	Very Rare
Skin & Subcutaneous Tissue Disorders	Contusions	Common
Musculoskeletal & Connective Tissue Disorders	Arthralgia	Very Rare

Hoarseness and candidiasis of the mouth and throat (thrush) occurs in some patients. Such patients may find it helpful to rinse out their mouth with water after using the inhaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with Flixotide Evohaler.

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decreased bone mineral density (see section 4.4).

As with other inhalation therapy, paradoxical bronchospasm may occur (see section 4.4). This should be treated immediately with a fast-acting inhaled bronchodilator. Flixotide Evohaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

There was an increased reporting of pneumonia in studies of patients with COPD receiving FLIXOTIDE 500 micrograms. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute: Inhalation of the drug in doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not necessitate emergency action being taken. In these patients treatment with fluticasone propionate by inhalation should be continued at a dose sufficient to control asthma adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis occurring in children exposed to higher than approved doses (typically 1000 micrograms daily and above), over prolonged periods (several months or years); observed features included hypoglycaemia and sequelae of decreased consciousness and/or convulsions. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery, infection or any rapid reduction in dosage.

Chronic: refer to section 4.4: risk of adrenal suppression.

Monitoring of adrenal reserve may be indicated. Treatment with inhaled fluticasone propionate should be continued at a dose sufficient to control asthma.

Treatment
Patients receiving higher than approved doses should be managed closely and the dose reduced gradually.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Fluticasone propionate given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs, resulting in a reduction of both symptoms and exacerbations of asthma, with a lower incidence and severity of adverse effects than those observed when corticosteroids are administered systemically.

Fluticasone propionate containing medications in asthma during pregnancy

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate combination relative to non-fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester inhaled corticosteroids-exposed pregnancies, 131 diagnosed major congenital malformations s were identified; 1612 (30%) were exposed to fluticasone propionate or salmeterol-fluticasone propionate of which 42 diagnosed major congenital malformations were identified. The adjusted odds ratio for major congenital malformations diagnosed by 1 year was 1.1 (95%CI: 0.5 – 2.3) for fluticasone propionate exposed vs non-fluticasone propionate inhaled corticosteroids exposed women with moderate asthma and 1.2 (95%CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of major congenital malformations was identified following first trimester exposure to fluticasone propionate alone versus salmeterol-fluticasone propionate combination. Absolute risks of major congenital malformations across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 major congenital malformations events per 100 pregnancies).

5.2. Pharmacokinetic Properties

In healthy subjects the mean systemic bioavailability of Flixotide Evohaler is 28.6%. In patients with asthma (FEV_1 < 75% predicted) the mean systemic absolute bioavailability was reduced by 62 %. Systemic absorption occurs mainly through the lungs and has been shown to be linearly related to dose over the dose range 500 to 2000 micrograms. Absorption is initially rapid then prolonged and the remainder of the dose may be swallowed.

Absolute oral bioavailability is negligible (< 1%) due to a combination of incomplete absorption from the GI tract and extensive first-pass metabolism.

87-100% of an oral dose is excreted in the faeces, up to 75% as parent compound. There is also a non-active metabolite.

After an intravenous dose, fluticasone propionate is extensively distributed in the body. The very high clearance rate indicates extensive hepatic clearance.

5.3 Preclinical safety data

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses greatly in excess of that proposed for therapeutic use. No novel effects were identified in repeat dose toxicity tests, reproductive studies or teratology studies. Fluticasone propionate is devoid of mutagenic activity *in vitro* and *in vivo* and showed no tumorigenic potential in rodents. It is both non-irritant and non-sensitising in animal models.

Subcutaneous embryofetal development studies in mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to 4 and 6 times the maximum recommended daily inhaled dose of 500 mcg twice daily in adults based on mouse and rat plasma levels of 486 and 710 pg/mL, respectively) resulted in fetal developmental toxicity characteristic of a potent corticosteroid, including cleft palate and embryonic fetal growth retardation, at doses that caused maternal toxicity. The no effect level for these finding in rat were associated with systemic exposures approximately 3 times the highest clinical exposure based on rat plasma level of 310 pg/mL. In the rabbit, fetal weight reduction and cleft palate occurred at a maternally toxic subcutaneous dose of 4 mcg/kg (less than 1.4 times the maximum recommended inhaled dose of 500 mcg twice daily based on rabbit plasma level of 149 pg/mL). However, fluticasone propionate administered via inhalation to rats did not induce teratogenicity at maternal toxic doses associated with exposures 17 times the human exposure achieved with the maximum recommended daily inhaled dose based on rat plasma level of 1890 pg/mL.

No evidence of impairment of fertility occurred in fertility studies in male and female rats at subcutaneous doses of fluticasone propionate up to 50 mcg/kg/day (approximately 6 times the human exposure associated with the maximum recommended daily inhaled dose of 500 mcg twice daily (110 pg/mL), based on rat plasma levels of approximately 650 pg/mL).

The non-CFC propellant, HFA 134a, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

The use of HFA 134a as a propellant has not altered the toxicity profile of fluticasone propionate compared to that using the conventional CFC propellant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HFA 134a

6.2. Incompatibilities

None reported.

6.3. Shelf Life

24 months

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze. Protect from frost and direct sunlight.
As with most medicines in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.
Pressurised container. Do not expose to temperatures higher than 50°C.
The canister should not be punctured, broken or burnt even when apparently empty.
Replace the mouthpiece cover firmly and snap into position.

6.5 Nature and contents of container

An inhaler comprising an aluminium alloy can sealed with a metering valve, actuator and dust cap. Each canister contains 120 metered actuations of 50 micrograms of fluticasone propionate (60 metered actuation hospital packs are available). Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The aerosol spray is inhaled through the mouth into the lungs. After shaking the inhaler, the patient should exhale, the mouthpiece should be placed in the mouth and the lips closed around it. The actuator is depressed to release a spray, which must coincide with inspiration of breath.

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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