4.3. Contraindications

Rosacea.
Acne vulgaris.
Perioral dermatitis.
Primary cutaneous viral infections (e.g., herpes simplex, chickenpox).
Hypersensitivity to any of the ingredients.
Perianal and genital pruritus.

The use of fluticasone propionate cream, ointment and emulsion is not indicated in the treatment of primary infected skin lesions caused by infection with fungi or bacteria.

Dermatoses in infants under three months of age, including dermatitis and napkin eruptions.

4.4. Special warnings and precautions for use

Prolonged application of high doses to large areas of body surface, especially in infants and small children, might lead to adrenal suppression. Children and infants have a greater surface area to body weight ratio compared with adults. Therefore, in comparison with adults, children and infants may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. Care should be taken when using fluticasone propionate cream, ointment and emulsion to ensure the amount applied is the minimum that provides therapeutic benefit.

The face, more than other areas of the body, may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematosus and severe eczema.

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye so as to avoid the risk of local irritation or glaucoma.

Topical steroids may be hazardous in psoriasis for a number of reasons, including rebound relapses, development of tolerances, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin. If used in psoriasis careful patient supervision is important.

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and systemic administration of antimicrobial agents.

Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressing, and so the skin should be cleansed before a fresh dressing is applied.
Cream and Ointment:

Overt suppression of the HPA-axis (morning plasma cortisol less than 5 micrograms/dL) is very unlikely to result from therapeutic use of fluticasone propionate Cream or Ointment unless treating more than 50% of an adult's body surface and applying more than 20 g per day for up to 3 weeks.

Cream and Emulsion:

Fluticasone propionate cream and emulsion may contain the excipient imidurea which releases traces of formaldehyde as a breakdown product.

Formaldehyde may cause allergic sensitization or irritation upon contact with the skin.

4.5. Interactions with other medicinal products and other forms of interaction

None reported

4.6. Pregnancy and Lactation

Pregnancy

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. The relevance of this finding to human beings has not been established; however, 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 foetus.

Lactation

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 milk. However plasma levels in patients following dermal application of fluticasone propionate at recommended doses are likely to be low.

4.7. Ability to perform tasks that require judgement, motor or cognitive skills

None reported.

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) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The background rates in placebo and comparator groups were not taken into account when assigning frequency categories to adverse events derived from clinical trial data, since these rates were generally comparable to those in the active treatment group. Rare and very rare events were generally derived from spontaneous data.
Infections and infestations

Very rare: Secondary infection.

Secondary infection, particularly when occlusive dressings are used or when skin folds are involved have been reported with corticosteroid use.

Immune system disorders

Very rare: Hypersensitivity.
If signs of hypersensitivity appear, application should stop immediately.

Endocrine disorders

Very rare: Features of hypercortisolism.

Prolonged use of large amounts of corticosteroids, or treatment of extensive areas, can result in sufficient systemic absorption to produce the features of hypercortisolism. This effect is more likely to occur in infants and children, and if occlusive dressings are used. In infants, the napkin may act as an occlusive dressing (see Warnings and Precautions).

Vascular disorders

Very rare: Dilation of superficial blood vessels.

Prolonged and intensive treatment with potent corticosteroid preparations may cause dilation of the superficial blood vessels.

Skin and subcutaneous tissue disorders

Cream and Ointment:

Common: Pruritus.
Uncommon: Local burning.

Emulsion:

Common: Local burning
Uncommon: Pruritus.

Cream, Ointment and Emulsion:

Very rare: Thinning, striae, hypertrichosis, hypopigmentation, allergic contact dermatitis, exacerbation of dermatoses, pustular psoriasis.

Local burning and pruritus have been reported, however in clinical trials the incidence of these adverse reactions was generally comparable to placebo and comparator groups.

Prolonged and intensive treatment with potent corticosteroid preparations may cause local atrophic
changes in the skin such as thinning, striae, hypertrichosis and hypopigmentation.

Exacerbation of the signs and symptoms of the dermatoses and allergic contact dermatitis have been reported with corticosteroid use.

Treatment of psoriasis with a corticosteroid (or its withdrawal) may provoke the pustular form of the disease.

4.9. Overdose Symptoms and Signs

Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse the features of hypercortisolism may appear.

Treatment

In this situation topical steroids should be discontinued gradually under medical supervision because of the risk of adrenal insufficiency.
Fluticasone Propionate (Inhaled Formulations)
Proposed Core Safety Profile (CSP)
for the PSUR worksharing scheme
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.

Inhaler, Evohaler, Accuhaler/Diskus and Rotadisk:

Fluticasone propionate is for inhalation by oral inhalation only.

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

Nebules:

Fluticasone propionate Nebules should be administered as an aerosol produced by a jet nebuliser, as directed by a physician.

Fluticasone propionate for nebulisation should not be injected.

Fluticasone propionate for nebulisation is intended for oral inhalation.

Patients should be given an initial dose of nebulised fluticasone propionate which is appropriate for the severity of their disease. The dosage should then be adjusted until control is achieved or reduced to the minimum effective dose according to the individual response.

4.3. Contraindications

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.

Increasing use of short-acting inhaled beta 2-agonists to control asthma symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

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.

Fluticasone propionate is not for use in acute asthma attacks, but for routine long-term management. Patients will require a fast- and short-acting inhaled bronchodilator to relieve acute asthmatic symptoms.

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.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see Overdosage). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma 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 titrated to the lowest dose at which effective control is maintained (see Adverse Reactions).

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

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

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled fluticasone propionate therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.

Similarly replacement of systemic steroid treatment with inhaled therapy may unmask 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.

Treatment with fluticasone propionate should not be stopped abruptly.

There have been very rare reports of increases in blood glucose levels (see Adverse Reactions) and this should be considered when prescribing to patients with a history of diabetes mellitus.

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 Interactions).

**Metered Dose and Dry Powder Inhalers:**

The possibility of impaired adrenal response should always be borne in mind in emergency situations, including surgery, and elective situations likely to produce stress
and appropriate corticosteroid treatment must be considered (see Overdosage).

Adrenal function and adrenal reserve usually remain within the normal range on recommended doses of fluticasone propionate therapy. The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids. However, the possibility of adverse effects in patients, resulting from prior or intermittent administration of oral steroids, may persist for some time. The extent of the adrenal impairment may require specialist advice before elective procedures.

# There was an increased reporting of pneumonia in studies of patients with COPD receiving FP 500 micrograms (see Adverse Reactions). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

Metered Dose Inhalers:

Patients' inhaler technique should be checked to make sure that inhaler actuation is synchronised with inspiration to ensure optimum delivery of the drug to the lungs.

Solutions for Nebulisation:

Fluticasone propionate Nebules are not for use alone in the relief of symptoms arising from acute bronchospasm when a short-acting inhaled bronchodilator (e.g. salbutamol) is also required. Fluticasone propionate Nebules are intended for regular daily treatment and as anti-inflammatory therapy in acute exacerbations of asthma.

Adrenal function and adrenal reserve usually remain within the normal range on recommended doses of fluticasone propionate therapy. The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids. However, the possibility of adverse effects in patients, resulting from prior or intermittent administration of oral steroids, may persist for some time. The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of impaired adrenal response should always be borne in mind in emergency situations, including surgery, which are likely to produce stress and appropriate corticosteroid treatment must be considered.

Severe asthma requires regular medical assessment, as it could be life-threatening. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Fluticasone propionate Nebules are not a substitute for injectable or oral corticosteroids in an emergency situation.

Patients receiving treatment with nebulised fluticasone propionate must be warned that if their clinical condition deteriorates they should not increase the dose or the frequency of administration, but should seek medical advice.

It is advisable to administer the nebulised fluticasone propionate via a mouthpiece to avoid the possibility of atrophic changes of facial skin which may occur with prolonged use with a face-mask.

When a face mask is used, the exposed skin should be protected by use of barrier cream or by thorough washing of the face after use.
Prolonged therapy with inhaled fluticasone propionate Nebules should be reduced gradually, and not be stopped abruptly, other than under medical supervision.

4.5. **Interactions 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.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled 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.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

4.6. **Pregnancy and Lactation**

**Pregnancy**

There is inadequate evidence of safety of fluticasone propionate in human pregnancy. 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. Tests for genotoxicity have shown no mutagenic potential.

However, as with other drugs the 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 foetus.

**Lactation**

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.
4.7. Ability to perform tasks that require judgement, motor or cognitive skills

Fluticasone propionate is unlikely to produce an effect.

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), and 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.

Infections and infestations

Very common: Candidiasis of mouth and throat.

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 their medication. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with fluticasone propionate.

Common: Pneumonia (in COPD patients)

Immune system disorders

Hypersensitivity reactions with the following manifestations have been reported:

Uncommon: Cutaneous hypersensitivity reactions.

Very rare: Angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactic reactions.

Endocrine disorders

Possible systemic effects include (see Warnings and Precautions):

Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma.

Metabolism and nutrition disorders

Very rare: Hyperglycaemia.
Psychiatric disorders

**Very rare** Unknown: Anxiety, sleep disorders, and behavioural changes, including hyperactivity and irritability (predominantly in children).

**Unknown:** Depression and aggression (predominantly in children).

Respiratory, thoracic and mediastinal disorders

Common: Hoarseness.

In some patients inhaled fluticasone propionate may cause hoarseness. It may be helpful to rinse out the mouth with water immediately after inhalation.

Very rare: Paradoxical bronchospasm.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Fluticasone propionate should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Skin and subcutaneous tissue disorders

Common: Contusions

4.9. Overdose

Symptoms and Signs

**Metered Dose and Dry Powder Inhalers:**

Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action, as normal adrenal function typically recovers within a few days.

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.

**Nebules:**

Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as
adrenal function is recovered in a few days, as verified by plasma cortisol measurements. However if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary. In cases of fluticasone propionate overdose, therapy may still be continued at a suitable dosage for symptom control.

Treatment

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