

FLUTICASONE



*“Vesuvius from Portici”, oil on canvas, 1774 - 76, Joseph Wright of Derby.
Huntington Library Pasadena*

We pursue all veins in the body of the Earth and live upon a hollow shell that we have made, and even so we are surprised at the earth opening up or trembling, as though it were not possible that these are her ways of showing anger at the maltreatment we inflict on her. We penetrate her innards and search for riches in the abode of the spirits of the dead as if the

Earth on which we walk were not sufficiently giving and fertile....Therefore in our souls....we must fry to realise when - after all these centuries - there is an end of draining her and how far we will go in our avarice. What an innocent happy, indeed even choice life we could live if only we strove for that which is above the Earth....

Pliny the Elder, "The Natural History", Book 33, 79 A.D

My uncle was stationed at Misenum, in active command of the fleet. On 24 August, in the early afternoon, my mother drew his attention to a cloud of unusual size and appearance. He had been out in the sun, had taken a cold bath, and lunched while lying down, and was then working at his books. He called for his shoes and climbed up to a place which would give him the best view of the phenomenon. It was not clear at that distance from which mountain the cloud was rising (it was afterwards known to be Vesuvius); its general appearance can best be expressed as being like an umbrella pine, for it rose to a great height on a sort of trunk and then split off into branches, I imagine because it was thrust upwards by the first blast and then left unsupported as the pressure subsided, or else it was borne down by its own weight so that it spread out and gradually dispersed. In places it looked white, elsewhere blotched and dirty, according to the amount of soil and ashes it carried with it. My uncle's scholarly acumen saw at once that it was important enough for a closer inspection, and he ordered a boat to be made ready, telling me I could come with him if I wished. I replied that I preferred to go on with my studies, and as it happened he had himself given me some writing to do.

As he was leaving the house he was handed a message from Rectina, wife of Tascus whose house was at the foot of the mountain, so that escape was impossible except by boat. She was terrified by the danger threatening her and implored him to rescue her from her fate. He changed his plans, and what he had begun in a spirit of inquiry he completed as a hero. He gave orders for the warships to be launched and went on board himself with the intention of bringing help to many more people besides Rectina, for this lovely stretch of coast was thickly populated. He hurried to the place which everyone else was hastily leaving, steering his course straight for the danger zone. He was entirely fearless, describing each new movement and phase of the portent to be noted down exactly as he observed them. Ashes were already falling, hotter and thicker as the ships drew near, followed by bits of pumice and blackened stones, charred and cracked by the flames: then suddenly they were in shallow water, and the shore was blocked by the debris from the mountain. For a moment my uncle wondered whether to turn back, but when the helmsman advised this he refused, telling him that Fortune stood by the courageous and they must make for Pomponianus at Stabiae. He was cut off there by the breadth of the bay (for the shore gradually curves round a basin filled by the sea) so that he was not as yet in danger, though it was clear that this would come nearer as it spread. Pomponianus had therefore already put his belongings on board ship, intending to escape if the contrary wind fell. This wind was of course full in my uncle's favour, and he was able to bring his ship in. He embraced his terrified friend, cheered and encouraged him, and thinking he could calm his fears by showing his own composure, gave orders that he was to be carried to the bathroom. After his bath he lay down and dined; he was quite cheerful, or at any rate he pretended he was, which was no less courageous.

Meanwhile on Mount Vesuvius broad sheets of fire and leaping flames blazed at several points, their bright glare emphasized by the darkness of night. My uncle tried to allay the fears of his companions by repeatedly declaring that these were nothing but bonfires left by the peasants in their terror, or else empty houses on fire in the districts they had abandoned....By this time the courtyard giving access to his room was full of ashes mixed with pumice stones, so that its level had risen, and if he had stayed in the room any longer he would never have got out. He was wakened, came out and joined Pomponianus and the rest of the household who had sat up all night. They debated whether to stay indoors or take their chance in the open, for the buildings were now shaking with violent shocks, and seemed to be swaying to and fro as if they were torn from their foundations. Outside, on the other hand, there was the danger of falling pumice stones, even though these were light and porous; however, after comparing the risks they chose the latter. In my uncle's case one reason outweighed the other, but for the others it was a choice of fears. As a protection against falling objects they put pillows on their heads tied down with cloths.

Elsewhere there was daylight by this time, but they were still in darkness, blacker and denser than any ordinary night, which they relieved by lighting torches and various kinds of lamp. My uncle decided to go down to the shore and investigate on the spot the possibility of any escape by sea, but he found the waves still wild and dangerous. A sheet was spread on the ground for him to lie down, and he repeatedly asked for cold water to drink. Then the flames and smell of sulphur which gave warning of the approaching fire drove the others to take flight and roused him to stand up. He stood leaning on two slaves and then suddenly collapsed, I imagine because the dense, fumes choked his breathing by blocking his windpipe which was constitutionally weak and narrow and often inflamed. When daylight returned on the 26th - two days after the last day he had been seen -- his body was found intact and uninjured, still fully clothed and looking more like sleep than death....

Pliny the Younger, letter to the Roman Historian, Tacitus c. 104 A.D

The period historians today call the Renaissance, represented one of the most astonishing periods of the cultural development of the West. Following the fall of the Western Roman Empire in 476 A.D, the West entered a protracted "Dark Age", where little scientific or cultural progress seemed to occur, all intellectual development held in relative stasis for close on eight centuries, by religious dogma and superstition. Although the term "Dark Ages" is today considered "politically incorrect", it is nonetheless entirely appropriate at least in relative terms. As William Manchester, wrote in his magisterial "A World Lit only by Fire" "Modern historians have abandoned that phrase, one of them writes, "because of the unacceptable value judgment it implies." Yet there are no survivors to be offended. Nor is the term necessarily pejorative. Very little is clear about that dim era. Intellectual life had vanished from Europe. Even Charlemagne, the first Holy Roman Emperor and the greatest of all medieval rulers, was illiterate..."

Around the Fourteenth century, the ancient knowledge, persevered largely in inaccessible form (to the West at least) at Constantinople and in the Islamic world began to be restored to the West, which took to its rediscovery with an insatiable thirst and an ungoverned curiosity. Over the next centuries the new learning would equal and then far surpass the ancients. This astonishing relearning would see its culmination in the Seventeenth century, as the "Age of Reason", or the great "Enlightenment"; and the birth of the age of science

as we know it today. By the Fourteenth century very little had survived. It was not simply the fall of Rome, there were many other factors, such as the disastrous loss of the great Library of Alexandria to fire and the rise of extreme religious dogma and oppression that contributed to the catastrophic collective loss of memory of the classical age. Records were fragmentary in the extreme - apart from a few great works which survived almost complete. Among these it was the works of the extraordinary Roman polymath and military commander, Pliny the Elder, (c.23- 79 A.D) that stand out as the greatest jewel in the crown of lost knowledge from a remote but fabulous age.

Pliny wrote three monumental works, each veritable encyclopedias that summarized virtually all knowledge in their fields. Tragically the first two works did not survive the early middle ages, 31 volumes on the History of Rome and 21 volumes dedicated specifically to the history of the early wars Rome fought in Germania. Fortunately his best work has survived, "The Natural History"; 37 priceless volumes. The only Roman "encyclopedia" of the natural world to survive to the present day, is rich in fascinating anecdotes which bring Pliny's times to vivid life. What is less well known about Pliny's work of "science" however is that ironically the last five volumes give us our only written record of Greek and Roman Art! Pliny describes the geology of the world not in dry terms of locations of mines or amounts of precious metals produced, but rather the uses to which these were put to in the Arts - most fascinating of all he gives rich descriptions not only of fabulous works of Art which were produced from the natural products of the earth, but of the Artists themselves, very famous in their day, and who without Pliny's work we would remain in complete ignorance of their existence. The greatest Artists of the early and high Renaissance studied Pliny's books on Art intensely, they laboured mightily to emulate the ancient world's achievements and above all to regain the lost prestige and exalted position that Art and the Artists themselves had once enjoyed, but had totally lost during the long ages of darkness, that came after the fall of Imperial Rome in the West.

Apart from Pliny's own "Natural History", we also know of him from his nephew, also a great writer. We know of Pliny the Elder's end in a poignant letter written by the younger Pliny and in this letter we have our only contemporary eye witness account of the eruption of Vesuvius and the destruction of Pompeii. In Pliny the Elder's 33rd book there is an astonishing passage that surely describes the first ever recognition of humanity's destruction of the environment. He rails against "luxuria" in particular the insatiable taste for expensive precious metals and the wanton raping of the Earth for these treasures. He warns of the dangers of ungoverned mining, that riddles the Earth's interior with mine shafts that he surmised would one day have disastrous consequences. It was irony in the extreme that the Earth itself would claim its only human advocate of that far distant age.

From Pliny the Younger's account we may glean that the elder Pliny probably suffered from chronic asthma, a condition which in all probability played a significant role in his death at the foot of Mount Vesuvius. There was nothing that could be done for asthma in the First Century A.D. In the Fourteenth century Pliny's words were rediscovered by the West, and these helped to spark the great relearning and the scientific method. Today we immeasurably benefit by this astonishing rebirth in all facets of our existence, not the least by our medicines such as the ubiquitous 21st century medication fluticasone which may have provided enough prophylactic protection to save one of the greatest polymaths ever to have lived.

FLUTICASONE

Introduction

Fluticasone propionate (trade name in Australia, “**Flixotide**”) is a **long acting** *inhalational* synthetic corticosteroid.

The low systemic bioavailability of fluticasone propionate provides a better risk/benefit outcome without the adverse effects that accompany long term systemically administered corticosteroids.

Fluticasone propionate has a marked anti-inflammatory effect in the lungs. It reduces symptoms and exacerbations of asthma.

Flixotide is not for use in acute attacks of bronchospasm, but for routine long-term management.

The onset of full therapeutic effect may take up to 4 - 7 days. ³

Chemistry

Fluticasone is a synthetic glucocorticoid

Classification

The inhaled corticosteroids include:

1. Beclomethasone
2. Budesonide
3. Ciclesonide
4. **Fluticasone**

The approximate dose equivalents for the treatment of asthma (may vary slightly according to source, and is not fully established for fluticasone furoate) are as follows:

100 micrograms beclomethasone is equal to:

- 200 micrograms budesonide
- 80 micrograms ciclesonide
- 100 micrograms fluticasone propionate
- 20 micrograms fluticasone furoate.

Preparations

Fluticasone propionate:

Mono-preparations:

- MDI, (metered dose inhaler) fluticasone propionate 50 mcg/dose.
- MDI, fluticasone propionate 125 mcg/dose.
- MDI, fluticasone propionate 250 mcg/dose.
- DPI, (dry powder inhaler) fluticasone propionate 100 mcg/dose.
- DPI, fluticasone propionate 250 mcg/dose.
- DPI, fluticasone propionate 500 mcg/dose.
- Nebules, fluticasone propionate 0.5 mg, 2 mL (single dose)
- Nebules, fluticasone propionate 2 mg, 2 mL (single dose)

Fixed dose combinations with salmeterol:

- MDI, (metered dose inhaler) Salmeterol 25 mcg, fluticasone propionate 50 mcg/dose
- MDI, Salmeterol 25 mcg, fluticasone propionate 125 mcg/dose
- MDI, Salmeterol 25 mcg, fluticasone propionate 250 mcg/dose
- DPI, (dry powder inhaler) Salmeterol 50 mcg, fluticasone propionate 100 mcg/dose
- DPI, Salmeterol 50 mcg, fluticasone propionate 250 mcg/dose
- DPI, Salmeterol 50 mcg, fluticasone propionate 500 mcg/dose

Fixed dose combinations with Eformoterol are also available.

Fluticasone furoate:

Fluticasone furoate as fixed dose combination with vilanterol:

There is also a **fluticasone furoate** preparation available.

Fluticasone furoate is **5 times more potent** than fluticasone propionate and can be given **once daily**.

This may be useful, e.g. for poorly compliant patients, but additional clinical benefits have not been shown. It is only available as a **fixed-dose combination with vilanterol**, a long-acting beta-2 agonist.

- DPI, fluticasone furoate 100 mcg, vilanterol 25 mcg (cap)
- DPI, fluticasone furoate 200 mcg, vilanterol 25 mcg (cap)

Mechanism of Action

Reduces airway inflammation and bronchial hyper-reactivity.

The corticosteroids **regulate gene expression**.

When a corticosteroid enters a cell, it combines with corticosteroid receptors in the cytoplasm.

This drug-receptor complex enters the nucleus where it controls synthesis of protein, including enzymes that regulate cell activity such as inflammation.

Pharmacodynamics

Fluticasone propionate given by inhalation at recommended doses has potent glucocorticoid activity in the airway.

Fluticasone propionate has a marked anti-inflammatory effect in the lungs. It reduces symptoms and exacerbations of asthma.

The potent anti-inflammatory action improves the symptomatic control of asthma, allows reduction of other drugs, such as rescue bronchodilators, and may limit the risk of decline in lung function over time.

The low systemic bioavailability of fluticasone propionate provides a better risk/benefit outcome without the adverse effects that accompany long term systemically administered corticosteroids.

The onset of full therapeutic effect may take up to 4 - 7 days.

Pharmacokinetics

Absorption:

- Fluticasone is administered by inhalation.

Fluticasone acts locally in the lungs - small amounts only are absorbed systemically from the lungs, (around 8- 10 %).

The bioavailability of the swallowed portion of an inhaled dose which reaches the gastrointestinal tract is virtually zero, the systemic absorption therefore is a reflection of the amount of drug that reaches the lungs.

Distribution

- Fluticasone propionate is extensively distributed within the body.

The volume of distribution at steady state is approximately 300 L

Metabolism and excretion:

- Fluticasone propionate is metabolized in the liver.

Indications

Indications include:

1. Preventive treatment of asthma in adults and children of age 1 year and older.
2. Preventive treatment of the reversible component of COPD

Contra-indications/precautions

Most contraindications to systemic corticosteroids are relative rather than absolute.

As inhaled corticosteroids have little systemic effects when used in appropriate dosing, these contraindications are even more relative for these agents.

For a list of the myriad contraindications/ precautions of orally administered corticosteroids see **Prednisolone (in the Drugs folder)**.

Pregnancy

Fluticasone propionate (and furoate) is a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Animal studies have shown that fluticasone may cause intrauterine growth restriction and congenital abnormalities. However, following human use of inhaled corticosteroids, there has been no evidence of an increased risk of small-for-gestational age, low birth weight, preterm birth or congenital malformations. Appropriate use of inhaled fluticasone has not been associated with adverse pregnancy outcomes.⁴

The pharmacological treatment of asthma during pregnancy should be the same as in non-pregnant women and should not be altered unless there is inadequate symptom control. Poorly controlled asthma during pregnancy increases the risk of adverse pregnancy outcomes. Therefore, use fluticasone during pregnancy if the patient has been stable on the medicine prior to conception or if it is considered the medicine of choice.⁴

The pharmacological treatment of asthma during pregnancy should be the same as in non-pregnant women and should not be altered unless there is inadequate symptom control. Poorly controlled asthma during pregnancy increases the risk of adverse pregnancy outcomes. Therefore, use fluticasone during pregnancy if the patient has been stable on the medicine prior to conception or if it is considered the medicine of choice.⁴

Note that salmeterol is also considered to be safe in pregnancy.⁴

Breast feeding

Fluticasone is safe in breastfeeding.

Published reports describing the use of fluticasone during breastfeeding have not been located. It is unknown whether fluticasone is excreted into breast milk, but inhaled fluticasone has limited systemic effects due to negligible oral bioavailability and rapid hepatic clearance. Therefore, inhaled corticosteroids are considered safe to use during breastfeeding.⁴

Note that salmeterol is also considered to be safe in breastfeeding.⁴

Adverse Effects

Inhaled steroids are designed to direct glucocorticoid delivery directly to the lungs in order to **reduce overall systemic glucocorticoid exposure and side effects.**

Consequently the adverse systemic effects of corticosteroids are **minimal** compared to corticosteroids that are administered orally.

However with **sufficiently high and prolonged dosing** all inhaled steroids can have adverse systemic effects.

Adverse local effects:

These include:

1. Hyper sensitivity reactions:

- As with other inhalation therapy, **paradoxical bronchospasm** may occur **rarely**, with an immediate increase in wheezing after dosing.

This should be treated immediately with a fast and short-acting inhaled beta-2 bronchodilator.

Flixotide should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted if necessary.

2. Candidiasis:

- Candidiasis of the mouth and throat (“thrush”) can occur in some patients.

Patients may find it helpful to rinse out their mouth with water after inhalation.

Symptomatic candidiasis can be treated with topical antifungal therapy while still continuing with the fluticasone propionate.

Rarely more serious oesophageal candidiasis can occur.

3. Dysphonia (i.e hoarseness of the voice):

- In some patients fluticasone may cause some dysphonia.

It may be helpful to rinse out the mouth with water immediately after inhalation.

Adverse systemic effects:

Systemic adverse effects will be minimal with the inhaled corticosteroids, but may theoretically occur if dosing is excessive and prolonged.

For the myriad systemic adverse effects of the corticosteroids - **as a group** - administered orally, see **Prednisolone (in Drugs folder)**.

Dosing

Flixotide is not for use in acute attacks of bronchospasm, but for routine long-term management.

Treatment with Flixotide should not be stopped abruptly.

For **fluticasone propionate**:

Adults and children over 16 years dosage range is 100 - 1000 microgram twice daily.

In general terms: ³

Mild asthma: 100 - 250 microgram twice daily.

Moderate asthma: 250 - 500 microgram twice daily.

Severe asthma: 500 - 1000 microgram twice daily.

Once asthma symptoms have been controlled, the dose of fluticasone propionate should be gradually reduced to the lowest dose which maintains control of asthma symptoms.



"The Last Day of Pompeii", oil on canvas, c. 1827-1833, Karl Briullov

References

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4. RWH Pregnancy & Breastfeeding Guidelines, 18 May 2016.

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