INTRODUCTION
Chronic Obstructive Pulmonary disease has long been defined by chronic bronchitis and emphysema, with patients being placed in one category or the other. This excluded the airflow obstruction which is predominant in COPD. Recent studies show different mechanisms of airflow obstruction: [1] loss of support of the small airways in emphysema, [2] chronic inflammation taking part in the smaller airways, and [3] presence of mucus in the small airways. COPD has now a more flexible definition of preventable and treatable disease with airflow limitation that is not fully reversible and an inflammatory response to noxious particles.

UPDATES ON THE MANAGEMENT OF COPD
Smoking still remains the primary culprit but with a more complicated association, since as reported in the literature, only 20-40% of those exposed to cigarette smoke develop COPD. Many patients in certain parts of the world have never smoked but have been exposed to wood flame during cooking. Thus, the etiology of COPD includes the effect of harmful agents, genetic predisposition, infectious agents and airway hyper-responsiveness.

Currently COPD is the 6th leading cause of death, but for the year 2020, it is estimated to be ranked third. This is partly being attributed to the gaining popularity of water pipe smoking (Fig. 1) amongst youths in the Middle East.

According to the WHO Study Group on Tobacco Product Regulation, a typical one hour-long session of water pipe smoking involves inhaling 100-200 times the volume of smoke inhaled by one cigarette.

LUNG FUNCTION DECLINE
Fletcher and Peto (Fig. 2) demonstrated that smokers have a more accelerated loss in lung function, which ultimately leads to symptomatic COPD. The loss of lung function is thought to be

Figure 1. A Middle-East water pipe
about 60 ml of forced expiratory volume in 1 second (FEV₁) per year, as compared to the normal loss of lung function, which is about 30 ml per year. This study⁴ showed that 15% of smokers are susceptible to COPD.

Recent studies report the proportion of smokers who are susceptible to COPD to be 30–40%. Anthonisen et al. found that people who quit smoking had a small loss of lung function of only 27 ml a year, as compared to those who continued to smoke, who lost about 60 ml per year.⁵ Regarding the ones who quit intermittently, the study found their loss of lung function comparable to those who never quit smoking, which means that smoking should be completely discontinued for patients to obtain the full benefit of doing so.

The most recent data is from the ECLIPSE study.⁶ The mean decline in lung function in smokers was actually less than expected, averaging approximately 33 ml per year, with only 38% of patients reaching a FEV₁ decline of more than 40 ml per year. The reasons behind this slow decline may be related to environmental conditions or treatment.⁷ This data suggests that treatment probably does have a positive impact on the lung function of COPD patients. There is increasing interest in the frequency of COPD exacerbations, since this was found to relate to prevention and treatment. Most of the new drugs being investigated and developed are targeting patients with the ‘frequent exacerbator’ phenotype.

The ECLIPSE data, showed that, depending on the overall Global Initiative for Obstructive Lung Disease (GOLD) stage, a significant proportion of patients had 2 or more exacerbations per year, and were thus defined as frequent exacerbators.⁸ More than 75% of treated patients in these studies were given long-acting bronchodilators and/or inhaled steroids. The method to identify the frequent exacerbators in clinical practice is their history. Other parameters that are helpful to identify these frequent exacerbators include having a more severe lung function, a worsening quality of life and a high white cell count.

An interesting finding is that having a history of gastroesophageal reflux disease (GERD) or heartburn seems to correlate with the development of COPD exacerbations.¹⁰ The pathogenesis of this is poorly understood, but may be related to a swallowing dysfunction. Although no studies have been conducted to evaluate whether treating these patients would help with COPD exacerbations, it is best to treat these patients with a trial of anti-reflux medicines.

Data from the COPD Gene study demonstrated that having chronic bronchitis doubles the frequency of COPD exacerbations.¹¹ Therefore, patients with a chronic bronchitis phenotype have a heightened risk and should be identified and followed-up closely. The COPD Gene study studied 10,000 people with COPD and conducted gene sequencing but it was not possible to identify a specific gene. In exacerbations one needs to consider other etiologies including pneumonia, congestive heart failure exacerbation, pulmonary emboli, as well as simply, non-compliance to prescribed medicines.¹²

The ECLIPSE study also reported that infections were responsible for approximately 50% of exacerbations. Haemophilus influenza along with Streptococcus pneumoniae and Moraxella catarrhalis were the most predominant. Patients with more severe disease were mainly affected by Pseudomonas infections. The role of Staphylococcus aureus and other Gram-negative bacteria is not well defined in exacerbations. It is also important to understand that some bacteria are colonizers and not actual pathogens. Previously, it was thought that COPD exacerbations were driven by a change in the concentration of bacteria; however, now we know that it is probably due to acquisition of new strains of bacteria.¹³

**MANAGEMENT**

The aim is to relieve symptoms, improve exercise tolerance and improve the overall health status. The main goals in the treatment of COPD include reducing the risks, preventing disease progression, preventing frequent exacerbations and reducing mortality. The pharmacological options in COPD are a growing field.¹⁴

Twenty years ago, the only treatment options were short-acting β-agonists, short-acting anti-muscarinics or a combination of both, in addition to theophylline and oral steroids. Nowadays, the list includes drugs such as long-acting bronchodilators (salmeterol, formoterol and once-daily indacaterol), inhaled corticosteroids (ICS) and phosphodiesterase inhibitors.

FEV₁ is no longer a comprehensive measurement of COPD disease. In a study by Westwood et al., there was a modest relationship between an increase in FEV₁, and improvements in the St George’s Respiratory Questionnaire. This means that treatment effectiveness can be assessed at a study level;¹⁵ however, from a practical point of view, this may be contradicted. For example, a patient may have an FEV₁ of 40%, yet their St George’s Respiratory Questionnaire score may be almost normal, compared to another patient with the same FEV₁ who is disabled and terribly symptomatic.

Other tests, besides measuring the lung function, give a better idea of the disease activity and severity. The BODE index,¹⁶ specific quality-of-life indices such as symptom rating scales, and also exercise testing can all give a better assessment.
Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing.

Trade Name: RELVAR ELLIPTA. Active Ingredients: 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). Pharmacological Form: 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed; pre-dispersed.

Indications: The 92 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta-agonist and inhaled corticosteroid) is appropriate.

Dosage and Method of Administration:

Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in lung function within 15 minutes of inhaling

Indications:

For Asthma:

Asthma is an ICS/LABA for patients (≥12 years)

Asthma use of a combination medicinal product (long-acting beta agonist and inhaled corticosteroid) is appropriate.

Dosage and Method of Administration:

Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents aged 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.

Precautions for Use:

Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD.

Drug Interactions:

Hypersensitivity to one or both active ingredients. Fluticasone furoate/vilanterol should not be used in patients with uncontrolled asthma but ‘as needed’ SABA1 when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta-agonist should be taken for immediate relief.

Overdose:


In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

Reporting Adverse Events (AEs):

Malta & Gibraltar: If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adportal

Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/
of the lung function. However, the limitations of these tests are that they are often difficult to perform in the clinic setting. The new GOLD guidelines recommend the Modified Medical Research Council Dyspnoea (MMRC) scale and the COPD Assessment Test (CAT) for use in the assessment of symptoms in COPD independently of FEV₁.

The UPLIFT study found that tiotropium, a bronchodilator, can actually cause a significant reduction of about 14% of exacerbations. A study performed by Calverley et al. compared formoterol–budesonide versus formoterol alone in the reduction of symptoms, and found that the combination of a long-acting β-agonist (LABA) with ICS reduces COPD symptoms on a daily basis. Further to this, the FLAME study showed that the combination LABA with a long-acting muscarinic antagonist (LAMA) (indacaterol-glycopyrronium) showed consistent superiority to LABA-ICS (salmeterol-fluticasone) for outcomes of exacerbations, lung function and health status. Thus, it is important not to have strict categorization of these drug classes. There are also multiple new drugs that do not act on the symptoms but have a significant impact on reducing exacerbations, such as the recently introduced oral phosphodiesterase inhibitor, roflumilast.

**HOW HAVE THE GUIDELINES CHANGED?**

COPD is no longer measured just by using spirometry and FEV₁. The full picture should take in account the assessment of symptoms and exacerbations. Associated co-morbidities, which are potential factors, also need to be included in the patients’ assessment.

Subsequently, the best assessment of COPD is to combine FEV₁ and symptom severity (Fig. 3). In summary, group A has an FEV₁ that is still above 50%, exacerbations that are not frequent and they are generally not symptomatic.

Group B is the same, except that they have more symptoms. Group C has a lower FEV₁, along with frequent exacerbations or symptoms, whereas group D combines all parameters.

The difficulty arises in deciding on the pharmacological treatment for each group. Generally, group A patients receive short-acting bronchodilators, whereas group B must be given LAMA or a LABA, and groups C and D should take an ICS in combination.

**CONCLUSION**

The disease progression of COPD should be explained to patients to help them overcome the denial of the causality of smoking. It is very important for patients to stay active; patients with symptomatic airflow obstruction should be offered a rehabilitation program as part of an optimal treatment plan.

It is difficult to treat dyspnoea or completely eliminate it, and this can require the use of double combinations of bronchodilators, i.e. LAMA plus LABA. If the patient does not respond, then a triple combination is recommended, with the addition of ICS. Some patients still do not improve, and one should consider adding a low dose of theophylline. Sometimes, nebulized bronchodilators may help as a back-up management. The last resort remains the use of chronic oral corticosteroids; however, this is discouraged due to the side-effects.

When the problem relates to recurrent exacerbations, a combination of ICS plus LABA / phosphodiesterase inhibitor may be used, as well as the addition of prophylactic antibiotics.
HEAD TO HEAD, DUAC WORKS FASTER THAN ERYTHROMYCIN-ZINC COMPLEX¹

- More patients with mild to moderate acne achieved at least a 30% reduction in inflammatory and non-inflammatory lesion counts at week 2 with Duac than Erythromycin-zinc complex¹
- DUAC demonstrated a faster onset of action, reducing total lesion count in significantly more patients than Erythromycin-zinc complex at just 2 weeks¹
- Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE²

**YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE**
Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance³:

- Thoroughly wash the affected area of skin
- Gently pat dry
- Apply a thin layer of Duac gel on the affected area, not just the individual spots

**TIPS**
If your patient’s skin peels or becomes dry, they can try:
- Using Duac less often, or stopping for one or two days before starting again
- Using an oil and fragrance-free hypoallergenic moisturiser
- If your patient’s skin becomes dry, they can try:
  - Using an oil and fragrance-free hypoallergenic moisturiser
  - Using Duac less often, or stopping for one or two days before starting again

Duac® Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above²

- **Active Ingredients**: Clindamycin phosphate/anhydrous benzoyl peroxide
- **Pharmacological Form**: 10mg/g + 50mg/g gel
- **Indication**: Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. Posology and Method of Administration: Cutaneous use only. Adults and Adolescents: Once daily in the evening. Treatment should not exceed more than 12 weeks. Elderly: No specific recommendations. Contraindication: Hypersensitivity to active substances, lincomycin and any of the excipients. Precautions for Use: Avoid Contact with the mouth, eyes, lips, other mucous membranes or area of irritated/broken skin. Use with caution in patients with a history of neurological, ulcerative colitis and antibiotic-associated colitis. If significant diarrhoea occurs or patients suffer from abdominal cramps, treatment should be immediately discontinued. Resistance to clindamycin: Patients with a recent history are more likely to have pre-existing anti-microbial resistant Propionobacterium acne and commensal flora. Cross-resistance: May occur when using antibiotic monotherapy. Fertility, Pregnancy and Lactation: There is no adequate data. Avoid application of the product to the breast area. Effect on Ability to Drive or Use Machines: No studies. Side Effects: Very Common side effects (at least 1 in 10): include erythema, peeling and dryness. Common side effects (less than 1 in 10): include burning sensation, photosensitivity and headache. Overdose: No specific antidote. Treatment should consist of appropriate symptomatic measures or clinically managed.

**REPORTING ADVERSE EVENTS (AEs):**
If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Gżira QRM 2416, Malta (Tel: +356 21239133)

Any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADR) reporting system: Details can be downloaded from www.medicinesauthority.gov.mt/adportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rte D’Argens, Gżira (ZRI) 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt


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www.hcp.gsk.com.mt/products/list/duac.html

For more information

Job no: MLT_GIB/CPB/1001/15a Date of preparation: October 2016
THE DISEASE PROGRESSION OF COPD SHOULD BE EXPLAINED TO PATIENTS TO HELP THEM OVERCOME THE DENIAL OF THE CAUSALITY OF SMOKING

REFERENCES