Manufacturer Submission

To

The National Institute for Health and Clinical Excellence

By

GlaxoSmithKline UK

Inhaled Corticosteroids for the Treatment of Chronic Asthma in Adults & Adolescents aged 12 years & over

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1 Executive Summary

1.1 Background

- Asthma is a chronic disease causing inflammation and constriction of the airways, leading to breathing difficulties. Asthma is one of the most common chronic diseases, affecting an estimated 300 million people around the world.
- The UK has one of the highest rates of asthma in the world. Asthma UK estimates that more than 3.7 million adults (aged 16 and over) in England and Wales have asthma.
- Survey and audit data suggest that the majority of adult asthma patients are likely to be uncontrolled. Poor asthma control is likely to cost the NHS at least three times more than well controlled asthma. Adherence is likely to be a significant contributor to poor asthma control.
- GlaxoSmithKline (GSK) manufactures two inhaled corticosteroids (ICSs), *Becotide®/Becodisks®/Becloforte®* (beclometasone dipropionate or BDP) and *Flixotide®* (fluticasone propionate or FP), licensed for the management of chronic asthma. Where therapy with both an ICS and long-acting β_2-agonist (LABA) is appropriate, a combination inhaler containing FP and salmeterol xinafoate (*Seretide®*) is available. All three ICS-containing preparations are available in a range of devices and doses as appropriate for patients.

1.2 Clinical Effectiveness & Safety

- Four research questions are addressed in this submission based on the comparisons in the appraisal scope and advice from clinical experts. The evidence to address these questions was identified from a systematic search of GSK internal data sources and additional searches of the published literature. 40 separate trials were used to address these questions and meta-analysis was used where appropriate to synthesise the data.

1.2.1 For patients taking ICS alone, is FP the most clinically effective ICS? (Question 1)

- FP is at least as effective as BDP, when used at half the dose, and may offer additional benefits in terms of lung function across all doses in patients who require treatment with an ICS alone.
- Treatment with high dose FP allows some patients to reduce or even stop taking oral corticosteroids whilst maintaining asthma stability.
- FP has no effect on markers of bone density and adrenal suppression in the majority of studies, at licensed doses. Where FP has an effect on bone density it is less detrimental than that of BDP.

1.2.2 For patients uncontrolled on ICS alone, is switching to *Seretide* more clinically effective than remaining on the same dose or increasing the dose of ICS alone? (Question 2)

- For patients uncontrolled on a range of ICSs, switching to *Seretide* achieves a more rapid and significantly better level of control; improving lung function and increasing the number of symptom-free days compared with remaining on an equivalent dose of ICS alone. This result is consistent across a range of severities.
- In addition, across all severities for patients uncontrolled on a range of ICSs, a more rapid and significantly better level of control is achieved by switching to

Seretide at an equivalent ICS dose than by increasing the dose of ICS; with improvements in a range of markers of asthma control including morning peak flow and the number of symptom-free days. This enables patients to achieve a better level of control at a lower dose of ICS.

1.2.3 Where a LABA and ICS are to be co-prescribed, is *Seretide* more clinically effective than ICS and LABA delivered in separate inhalers? (Question 3)

- Randomised clinical trials comparing *Seretide* and its components were powered to demonstrate equivalent efficacy. In general, *Seretide* is at least as efficacious as FP plus salmeterol xinafoate (SX) with trends towards better efficacy.
- However, these studies were all double blind, double dummy in design and therefore any benefits resulting from improved adherence due to the use of a single inhaler would not be captured.
- Poor adherence with asthma medication is acknowledged to be a significant clinical issue and may lead to worse outcomes for patients and therefore be a significant barrier to achieving control.
- Observational studies are a more appropriate study design to measure adherence benefits. Available observational data suggest that *Seretide* is associated with improved adherence compared with separate inhalers, which may lead to improved outcomes such as reduced oral corticosteroid and short-acting β_2-agonist (SABA) use.

1.2.4 In patients where combination therapy is appropriate what is the relative clinical effectiveness of *Seretide* compared with Symbicort™? (Question 4)

- The most appropriate way to compare the clinical efficacy of *Seretide* and Symbicort in line with the appraisal scope is to review head-to-head studies comparing equivalent dosing regimens. There are relatively few studies available of this type, but those that exist suggest *Seretide* and Symbicort achieve similar levels of efficacy. Other head-to-head studies comparing *Seretide* and Symbicort in non-equivalent dose management strategies are not reviewed as these address questions outside the appraisal scope.
- *Seretide* offers more choice to patients in the type of device. It is available in both a metered dose inhaler (MDI) and a dry powder inhaler (DPI), across the range of indicated doses, thereby enabling the patient and their prescriber to choose the most appropriate device for them.

1.3 Cost effectiveness of *Seretide*

- A two-state one year model was used to estimate the cost effectiveness of *Seretide* compared with the same and increased dose of ICS alone, concurrent ICS and LABA, and Symbicort. Estimates of effectiveness were assessed using a synthesis of data on symptom-free days from direct head-to-head trials. The costs and utility associated with each model state were estimated from a large randomised controlled trial.
- For questions 2 and 3, *Seretide* was compared with FP and FP plus SX components respectively as the base case. Sensitivity analyses against BDP plus SX used BDP prices, but as a conservative approach the clinical effectiveness of BDP was assumed to be the same as FP.

1.3.1 For patients uncontrolled on ICS alone, is switching to *Seretide* more cost effective than remaining on the same dose or increasing the dose of ICS alone? (Question 2)

- The incremental cost effectiveness ratio (ICER) for *Seretide* compared with same dose FP across the low, medium and high dose comparisons is lower than the £30,000 per QALY (Quality Adjusted Life Year) cost effectiveness threshold (ranging from £3,660 to £29,534). In a sensitivity analysis using the costs of BDP, *Seretide* remains cost effective at the low and medium doses (ranging from £9,254-£24,020) and at high doses the *Seretide Accuhaler*® provides a cost effective option (£18,034-£24,143).
- For the comparison with increased dose FP, *Seretide* is shown to be cost effective at both the dose comparisons undertaken (low and medium), either dominating the comparator or with ICERs well below the £30,000 threshold (ranging from £51 to £9,196). *Seretide* remains cost effective in a sensitivity analysis using the costs of BDP (ranging from £3,568 to £15,997).

1.3.2 Where a LABA and ICS are to be co-prescribed, is *Seretide* more cost effective than ICS and LABA delivered in separate inhalers? (Question 3)

- From the clinical trial evidence there is little to distinguish *Seretide* from ICS plus LABA in separate inhalers in clinical terms, but the balance of evidence suggests that *Seretide* is generally more cost effective. In addition, these cost effectiveness ratios do not include the potential improved patient benefits that may result from better adherence when using only one inhaler given the double blind, double dummy nature of the studies involved.

1.3.3 In patients where combination therapy is appropriate, what is the relative cost effectiveness of *Seretide*? (Question 4)

- *Seretide* dominates Symbicort 200/6 at the medium dose, as it is cheaper and slightly more effective (in percentage symptom-free days) using equivalent dose regimens.
- No conclusions on the cost effectiveness of *Seretide* compared with Symbicort at the low and high doses could be made because of a lack of appropriate trial data.
- Comparing costs only there is a cheaper *Seretide* option available at all doses.

1.4 NHS budget impact

- Switching 50 percent of uncontrolled asthmatic patients aged 12 and over currently treated with ICS alone to *Seretide* results in a total increase of £18.3 million in drug costs in the first year (£34,589 per 100,000 population) in England and Wales. This represents approximately three percent of the total estimated annual drug costs of asthma for the UK.
- The first year budget impact of an alternative treatment strategy of increasing the ICS dose for 50 percent of patients whose asthma is uncontrolled is estimated to be £6.8 million in England and Wales, but this is not a licensed therapeutic strategy for all patients. If all switching patients step up therapy (including on to unlicensed therapies) the total budget impact of the increased dose ICS option increases to between £7.9 and £8.3 million in the first year.
- Given that improving asthma control is an important objective of treatment guidelines, the additional cost of achieving these benefits could be partly offset by savings from switching from separate inhalers of ICS and LABA and Symbicort to *Seretide*.

- For example, if 50 percent of patients are switched from separate inhalers of ICS and LABA to *Seretide* there is a potential cost saving (£9.8 million).
- There is also a potential saving in switching patients to *Seretide* from Symbicort (£2.5 million if 50 percent of patients are switched).

1.5 Conclusions

- FP is at least as clinically effective as BDP and may have some additional benefits in terms of lung function and safety.
- The BTS/SIGN Asthma Guideline does not specify the ICS dose to add in a LABA and therefore at which to use *Seretide*. However, the findings presented in this submission show that for patients uncontrolled on BDP 400µg/day equivalent it is a cost effective option to switch to *Seretide* compared with increasing the dose of ICS and therefore should be the preferred therapeutic approach.
- For those patients who have already passed this point and are uncontrolled on BDP 800µg/day equivalent switching to *Seretide* remains a cost effective approach.
- Compared with separates, *Seretide* is at least as clinically effective and has other benefits such as adherence. In addition, *Seretide* is generally a cheaper option. Cost is therefore not a barrier and *Seretide* should be the preferred option to separates where a patient requires an ICS and LABA to be co-prescribed.
- The most appropriate way to compare *Seretide* and Symbicort in line with the appraisal scope is to review head-to-head studies comparing equivalent dosing regimens. There are relatively few studies available but those that exist suggest *Seretide* and Symbicort achieve similar levels of efficacy. There is, however, a cheaper *Seretide* option at all doses and *Seretide* offers more device choice to patients. Therefore, the evidence suggests that *Seretide* should be considered the preferred combination therapy.
- There are some budgetary implications of using *Seretide* for patients with uncontrolled asthma; however, it is a more cost effective approach. Savings to partly offset these costs could be made by switching from separates and from Symbicort to *Seretide*.