

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

Scientific conclusions

Overall summary of the scientific evaluation of Flutiform and associated names (see Annex I)

Flutiform 50/5, 125/5 and 250/10 microgram pressurised inhalation, suspension is a new fixed-dose combination of two well-known active drug substances fluticasone propionate and formoterol fumarate. It is intended for use in the management of asthma, formulated as a pressurised inhalation suspension in three strengths, and administered via a pressurised metered dose inhaler (pMDI).

Fluticasone propionate is an inhaled glucocorticosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Fluticasone propionate has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyperreactive airways.

Formoterol fumarate is a selective long-acting β_2 adrenergic agonist and exerts a preferential effect on β_2 adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Formoterol fumarate is used via the orally inhaled route in the management of patients with reversible airways obstruction. Following oral inhalation of formoterol the onset of bronchodilatation is rapid, within 1 - 3 minutes, and bronchodilatation following a single dose lasts for 12 hours. Formoterol fumarate is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid.

The products are orally inhaled products and the combined therapy of an inhaled glucocorticosteroid and a selective long-acting β_2 adrenergic agonist is well established for use in the regular treatment of adults and children with asthma where the use of such a combination is deemed appropriate. However, the specific formulation of a fixed-dose combination of these two well known active substances, fluticasone propionate and formoterol fumarate, is new.

The indication sought is the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and ‘as required’ inhaled short-acting β_2 agonist. [“Step-up” indication]

Or

- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist. [“Switch” indication]

The clinical development programme for Flutiform was set up to evaluate efficacy and safety in the intended patient population.

The total programme comprised 18 completed studies and included almost 5000 patients. The five pivotal Flutiform Phase III studies included approximately 2500 patients and the safety database includes over 1900 Flutiform-treated patients.

The pivotal clinical studies were designed to compare the efficacy and safety of Flutiform with its individual components administered separately and with its individual components administered together but inhaled from separate inhalers. Supportive studies compared the efficacy and safety of Flutiform with other combination therapies. The development programme also assessed the efficacy and safety of Flutiform administered either with or without a spacing device and investigated the efficacy and safety of Flutiform across relevant subgroups.

The objecting Member State stated that proof of similar control of inflammation by fluticasone in this new fixed-dose combination product compared with fluticasone as monotherapy or in combination with other long-acting β_2 agonists has not been established either in pharmacokinetic studies or in clinical studies. In both claimed indications the previously used inhaled corticosteroid (ICS) is replaced by the inhaled corticosteroid in Flutiform for which such proof is required.

Based on the results of the pharmacokinetic and clinical studies the objecting Member State stated that proof of equivalent bioavailability or control of inflammation is not established because:

- In the pharmacokinetic data presented systemic exposure of fluticasone was lower (67%) following Flutiform inhalation than following the concurrent inhalation of fluticasone and formoterol from monoproduct pMDIs.

The designs of the clinical studies were not appropriate to establish equivalent control of inflammation because in order to distinguish a potential difference between two ICS products, exacerbations (particularly severe exacerbations) are the indicated parameter. To distinguish a potential difference a study with a long duration e.g. 6-12 months is necessary. None of the submitted clinical trials were of such duration.

In the frame of the referral under article 29(4), the Applicant was requested to respond to the following: *“In the light of the available pharmacokinetic data showing a lower systemic exposure of the fluticasone propionate component of this fixed-dose combination product, there is concern that patients receiving this fixed-dose combination, whether for the 'substitution' indication or for the 'step-up' indication, may not experience the same level of efficacy in respect of long-term asthma control. The Applicant should discuss this concern in the light of the relatively short duration of the clinical study and the fact that the formoterol fumarate component in this fixed-dose combination might have masked a loss of control by controlling symptoms and bronchodilatation.”*

Pharmacokinetic (PK) data

The PK study (Study FLT1501) which has given rise to concerns was conducted to evaluate the comparative safety of Flutiform when compared with the marketed monoproduct pMDIs. Approximately 20 subjects in each arm of this parallel group study were administered Flutiform 500/20 (fluticasone propionate 500 μ g and formoterol fumarate 20 μ g) or GSK fluticasone propionate 500 μ g pMDI + Novartis formoterol fumarate 24 μ g pMDI. The relative bioavailability of fluticasone propionate at steady state was 67% following Flutiform administration compared with GSK fluticasone propionate pMDI.

The PK data in Study FLT1501 were compared with a corresponding pharmacodynamic (PD) dataset from Study FLT3503. These PK and PD studies both included the same strengths/doses of Flutiform, GSK fluticasone propionate pMDI and Novartis formoterol fumarate pMDI, and all products in both studies were administered via the same spacing device, so allowing a valid comparison of PK and PD data. This comparison showed that despite a lower relative fluticasone propionate bioavailability, the effect upon pre-dose FEV₁ (which was demonstrably mediated by fluticasone propionate alone in Study FLT3503) was numerically greater with Flutiform 500 μ g/20 μ g than with GSK fluticasone propionate 500 μ g (either alone or in conjunction with Novartis formoterol fumarate 24 μ g). The inclusion of a second, lower dose of Flutiform (100 μ g/10 μ g) in the PD study was also instructive. Effects with the low dose of Flutiform (100 μ g/10 μ g) upon pre-dose FEV₁ were similar to those with the high dose of GSK fluticasone propionate 500 μ g (alone or in combination with formoterol fumarate 24 μ g).

Literature data indicate that even if the PK data accurately reflect comparative pulmonary drug deposition for Flutiform versus GSK fluticasone propionate pMDI, such differences are not of clinical relevance. Furthermore, the discordance between the PK and PD data for Flutiform suggests that the PK data do not

accurately reflect comparative pulmonary deposition and are not a valid surrogate for clinical effect. The Applicant presented some reasons which could potentially explain such discordance: this could be a function of the deviation of orally inhaled product (OIP) pulmonary PK from standard PK principles, i.e. unlike conventional PK analysis (e.g. for tablets) blood concentrations of OIPs are a “post-event” (rather than “pre-event”) surrogate for efficacy and standard PK analysis does not necessarily define drug residence at the pulmonary site of action.

The CHMP noted that the differences of the magnitude observed between Flutiform and GSK fluticasone propionate in Study FLT1501 (67% relative bioavailability) are within the same range of variance as observed within patients (from inhalation to inhalation), between different batches of the same product and between different inhalers containing the same or more than one of the same active substances and are without adverse clinical consequences, and therefore are likely to be clinically irrelevant. In addition, the comparison of these PK data with PD data, Study FLT3503, shows that despite the lower relative bioavailability of fluticasone propionate in this new fixed-dose combination product the effect upon pre-dose FEV₁ (which was demonstrably mediated by fluticasone propionate alone in Study FLT3503) was numerically greater with Flutiform 500µg/20µg than with GSK fluticasone propionate 500µg (either administered alone or administered together with Novartis formoterol fumarate 24µg). Study FLT 3503 also included a comparison with a lower dose of Flutiform and effects seen with this lower dose of Flutiform (100µg/10µg) upon pre-dose FEV₁ were similar to those seen with the high dose of GSK fluticasone propionate 500µg (administered both alone or in combination with formoterol fumarate 24µg). The CHMP was of the opinion that these findings suggest that the PK data from study FLT1501 do not reflect pulmonary deposition accurately and therefore in this study are not a valid surrogate for clinical efficacy of Flutiform.

Furthermore, the CHMP noted that the need to demonstrate either pharmacokinetic equivalence or therapeutic equivalence to a reference product is not a requirement for this development, which was submitted according to Directive 2001/83/EC, Article 10b fixed combination application – requiring *complete administrative and complete quality, non-clinical and clinical data on the combination only*; the specific combination of these two well known active substances, fluticasone propionate and formoterol fumarate, is new, and therefore equivalence/therapeutic equivalence does not have to be proven.

Masking of any lesser clinical corticosteroid effect by the long-acting β_2 agonist

Of the five pivotal studies submitted with this Marketing Authorisation Application three studies were designed such that they facilitate a rigorous, internally validated examination as to whether the long-acting β_2 agonist formoterol fumarate “masks” deficient corticosteroid effects of Flutiform upon pre-dose FEV₁. This endpoint (i.e. change in FEV₁ from pre-dose at baseline) was designated *a priori* as the primary endpoint to assess corticosteroid effect.

The Applicant stated that the choice of this endpoint is consistent with the Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Asthma - CPMP/EWP/2922/01); it is accepted as an appropriate endpoint to measure inhaled corticosteroid effect as *per* the CHMP OIP Guideline (CPMP/EWP/4151/00 Rev.1); and it is advocated as an essential endpoint in asthma studies by a joint expert committee of the American Thoracic Society and European Respiratory Society (ATS/ERS).

Assessment of the pre-dose FEV₁ data in the three specified studies demonstrated that in two of the three studies formoterol fumarate has no effect upon pre-dose FEV₁ whilst in the third study there was some residual formoterol effect upon pre-dose FEV₁ but it was insufficient to explain the magnitude of the pre-dose FEV₁ treatment effect difference between Flutiform and fluticasone propionate pMDI.

The CHMP supported the clinical study designs in the Phase III clinical development programme and the use of pre-dose FEV₁ as the primary endpoint for efficacy in respect of corticosteroid effect. The

Committee was also of the opinion that the corticosteroid effects seen with Flutiform are no less than those seen with GSK fluticasone propionate pMDI and that formoterol fumarate does not appreciably “mask” any lesser corticosteroid effect. The apparent lower systemic availability of fluticasone propionate in Flutiform compared with GSK fluticasone propionate pMDI would not appear to result in a lesser clinical effect. The clinical findings suggest that fluticasone propionate in Flutiform is non-inferior in respect of clinical effects to GSK fluticasone propionate.

Asthma control and exacerbations

Asthma control is one of two principal treatment goals in asthma management (the other being the reduction of exacerbation risk). It is a multidimensional concept incorporating symptoms, night time awakenings, use of rescue medication, lung function and activity limitation. Several endpoints which reflect these different facets of asthma control are modulated by long-acting β -agonists.

Data submitted by the Applicant demonstrated that asthma control with Flutiform is superior to that with fluticasone propionate pMDI alone and that asthma control with Flutiform is similar to that with fluticasone propionate pMDI + formoterol fumarate pMDI. With regard to the duration of the pivotal studies (8-12 weeks), literature data support the view that treatment effects upon asthma control variables are maximal within 3 months and sustained thereafter. As such the applicant claimed that the asthma control results from the pivotal studies should logically be extrapolated to the longer-term.

The question posed by CHMP implied that the 67% relative bioavailability of the fluticasone propionate component of Flutiform compared with GSK fluticasone propionate pMDI may translate to a lesser inhaled corticosteroid effect and that this lesser effect would be best evaluated in a 6- to 12-month exacerbations study. This hypothesis has in turn led to concerns regarding the duration of the Applicant’s 8 to 12 week studies. Moreover it was proposed that “severe” exacerbations are the most discriminative exacerbations variable.

However, the Applicant has found no evidence to support such a view in the literature. In studies comparing a two-fold dose multiple of fluticasone propionate, dose response for exacerbations has never been shown. These include two published studies which specifically recruited patients with a history of recent exacerbations and which were conducted over 6 to 12 months (Ind 2003; Verona 2003). These results do not imply that modest differences in pulmonary inhaled corticosteroid delivery will result in differences in exacerbation risk.

With regard to the suggestion that “severe” exacerbations are the optimal variable with which to examine potential differences in inhaled corticosteroid effect, the applicant commented that literature does not support this view. Nor does the literature offer any support for the notion that the exacerbations captured within the Applicant’s clinical studies might not be adequate. The leading global expert respiratory group (ATS/ERS) has recently proposed standardised definitions of clinically relevant exacerbations for use in future trials. The exacerbations captured within the Applicant’s studies are consistent with those described by the ATS/ERS (although differences in terminology do exist).

Turning to the available data in the Applicant’s studies, for the “Step-up” comparison the odds of “any” exacerbation were 33% higher in fluticasone propionate- than Flutiform-treated patients ($p=0.019$) whilst the annual exacerbation rate was 49% higher in fluticasone propionate- than Flutiform-treated patients ($p=0.004$). These data were generated from the five pivotal 8- to 12-week studies and demonstrate the protective benefit of Flutiform against exacerbations compared with fluticasone propionate monotherapy. Published sources indicate that these treatment differences would at worst remain static and at best improve in favour of Flutiform over the longer-term.

With regard to the “Switch” indication, the proportion of patients experiencing exacerbations in the pivotal “Switch” study (Study FLT3503) was similar in Flutiform and fluticasone propionate + formoterol fumarate treated patients (36.4% and 35.3%, respectively) although this analysis lacked discriminative capacity as the proportion of fluticasone propionate monotherapy-treated patients experiencing exacerbations was similar (37.4%). However, an analysis of annualised exacerbation rates in this study was able to differentiate the effects of high dose ICS-LABA (inhaled corticosteroid - long-acting β_2 agonist) treatments (Flutiform 500 μ g/20 μ g and fluticasone propionate 500 μ g + formoterol fumarate 24 μ g) from low dose ICS-LABA treatment (fluticasone propionate 100 μ g/10 μ g) and fluticasone propionate 500 μ g monotherapy. An annual exacerbation rate ratio of 0.98, i.e. very close to unity for the comparison of Flutiform 500 μ g/20 μ g versus fluticasone propionate 500 μ g + formoterol fumarate 24 μ g was therefore suggestive of non-inferiority but was not statistically definitive. However the exacerbations data were supported by the nocturnal symptoms and discontinuations due to lack of efficacy data. These endpoints were demonstrably inhaled corticosteroid-driven and/or inhaled corticosteroid dose-responsive and all provided rigorous statistical evidence that the inhaled corticosteroid effects of Flutiform were not less than those of fluticasone propionate + formoterol fumarate. The pre-dose FEV₁ data in this study which were again a demonstrably inhaled corticosteroid-mediated effect provided no evidence of a lesser inhaled corticosteroid effect with Flutiform than seen with fluticasone propionate + formoterol fumarate.

With regard to the “Switch” therapy, the CHMP accepted the discussions presented by the Applicant and was of the view that the clinical effects of Flutiform in respect of asthma control and exacerbation risk are comparable with/similar to the clinical effects of GSK fluticasone propionate and Novartis formoterol fumarate given concomitantly.

The magnitude of changes seen on a range of secondary endpoints helps to quantify the clinical relevance of the effects seen on pulmonary function and on exacerbation rate. Across a broad range of endpoints such as discontinuation due to lack of efficacy, symptom-free days and nights and the amount of *rescue* medication, the size of effect seen is clinically important. These findings should be taken together with the results that show that the clinical effects of Flutiform are comparable with the clinical effects of GSK fluticasone propionate and Novartis formoterol fumarate given concomitantly. This provides further support for the clinical relevance of the effects seen with Flutiform.

With regard to the “Step-up” indication, again the CHMP accepted the discussions presented by the Applicant and was of the view that the clinical effects of Flutiform in respect of asthma control are superior to the clinical effects of GSK fluticasone propionate administered alone. The data presented in respect of exacerbations demonstrate an increased protective benefit of Flutiform compared with GSK fluticasone propionate administered alone – the odds of any exacerbation occurring were 33% higher and the annual exacerbation rate was 49% higher in patients receiving GSK fluticasone propionate than in patients receiving Flutiform, $p=0.019$ and $p=0.004$, respectively.

Predictive value of the FEV₁ data

To further address the concerns raised regarding the duration of the Applicant’s clinical studies and to supplement the exacerbations data and other clinical data, the Applicant reviewed the FEV₁ data and their predictive value.

In its recent Consensus Statement on Asthma Control and Exacerbations the ATS/ERS identified pre-dose FEV₁ as an essential endpoint in asthma studies and a predictor of future exacerbation risk. This recommendation was made on the basis of several published studies which have demonstrated the predictive value of pre-dose and random/post-dose FEV₁ over both the medium- and longer-term. The Applicant’s own short- and long-term studies have demonstrated the same association between FEV₁ and future exacerbation risk.

In addition to the above is the observation from several published studies that FEV₁ is maximal following approximately 8 to 12 weeks inhaled corticosteroid-based treatment and is stable thereafter. Again a similar pattern was evident from the Applicant's own long-term study.

Turning to the data in the Applicant's clinical studies: For the "Step-up" indication both pre-dose and post-dose FEV₁ effects at 8 to 12 weeks were significantly greater with Flutiform than with fluticasone propionate; for the "Switch" indication both pre-dose and post-dose FEV₁ effects numerically favoured Flutiform over fluticasone propionate + formoterol fumarate (in both Per Protocol and Intention-to-Treat population comparisons).

In conclusion, given the long-term predictive value of FEV₁, given the static nature of FEV₁ after 8 to 12 weeks of treatment, and given the pattern of the FEV₁ data observed in the five pivotal studies, the CHMP considers there to be no reason to anticipate that the long-term exacerbation risk with Flutiform may exceed that with fluticasone propionate alone (the "Step-up" indication) or fluticasone propionate in combination with formoterol fumarate (the "Switch" indication). These conclusions based on an indirect assessment of future exacerbation risk are consistent with and support those based on a direct observation of exacerbation rates during the clinical studies.

The CHMP was of the view that clinical data generated over 6 to 12 months to further elucidate the level of asthma control and to further assess exacerbation rates seen with Flutiform compared with fluticasone propionate administered concomitantly with formoterol fumarate or administered alone, are not required.

Grounds for positive opinion

Whereas

- The Committee considered the notification of the referral triggered by the United Kingdom under Article 29(4) of Council Directive 2001/83/EC.
- The Committee reviewed all available data submitted by the applicant to address the potential serious risk to public health, in particular the efficacy in respect of long-term asthma control.
- The Committee considered that the overall safety and efficacy have been sufficiently proven by the studies presented.
- Therefore the Committee concluded that the benefit-risk balance of Flutiform in the applied indications is favourable.

the CHMP has recommended the granting of the marketing authorisation for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Flutiform and associated names (see Annex I).