

28 June 2012  
EMA/399193/2012

## Assessment report pursuant to Article 29(4) of Directive 2001/83/EC, as amended

### **Flutiform and associated names**

INN of the active substance(s): Fluticasone propionate/Formoterol fumarate

Marketing authorisation holder: Napp Pharmaceuticals Ltd

Procedure no: EMEA/H/A-29/1326

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Background information on the procedure ..... 3

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure..... 3

1.2. Notification of an official referral for arbitration..... 3

2. Scientific discussion during the referral procedure..... 3

2.1. Introduction ..... 3

2.2. Critical evaluation ..... 4

2.3. Recommendation ..... 9

2.4. Conclusions and benefit risk assessment ..... 9

Appendix 1 ..... 10

Divergent positions ..... 10

# **1. Background information on the procedure**

## ***1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure***

Napp Pharmaceuticals Ltd submitted an application for decentralised procedure of Flutiform and associated names, 50 mcg/5 mcg, 125 mcg/5 mcg & 250 mcg/10 mcg pressurised inhalation, suspension on 25 March 2010.

The application was submitted to the reference Member State (RMS): United Kingdom and the concerned Member States (CMS) : Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovakia and Sweden.

The Decentralised procedure UK/H/2872/01-03/DC started on 15 June 2010.

All applications were withdrawn from the CMS Spain on 05 April 2011 prior to the initiation of day 106 of the DCP and therefore in accordance with Directive 2001/83/EC, Spain was no longer involved in the ongoing procedure.

On day 210, major issues on efficacy and bioequivalence raised by the Netherlands, remained unresolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by the United Kingdom on 21 October 2011. The CMD(h) 60 day procedure was initiated on 24 October 2011.

Day 60 of the CMD(h) procedure was on 22 December 2011, and since there could be no agreement the procedure was referred to the CHMP.

## ***1.2. Notification of an official referral for arbitration***

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by the United Kingdom on 22 December 2011. The Netherlands raised public health objections as a positive benefit-risk balance for the proposed indications has not been proven based on a combination of pharmaceutical and clinical data. Therapeutic equivalence of the fixed-dose combination, with respect to fluticasone propionate and formoterol fumarate has not been demonstrated by means of pharmacokinetic studies (lower systemic exposure of fluticasone propionate and formoterol with Flutiform) and clinical studies provide insufficient reassurance that the lower fluticasone propionate exposure has no impact on long-term asthma control.

# **2. Scientific discussion during the referral procedure**

## ***2.1. Introduction***

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  $\beta_2$  adrenergic agonist and exerts a preferential effect on  $\beta_2$  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  $\beta_2$  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  $\beta_2$  agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting  $\beta_2$  agonist. ["Step-up" indication]

Or

- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting  $\beta_2$  agonist. ["Switch" indication]

## **2.2. Critical evaluation**

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  $\beta_2$  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 500µg and formoterol fumarate 20µg) or GSK fluticasone propionate 500µg pMDI + Novartis formoterol fumarate 24µg 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 FEV<sub>1</sub> (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 alone or in conjunction with Novartis formoterol fumarate 24µg). The inclusion of a second, lower dose of Flutiform (100µg/10µg) in the PD study was also instructive. Effects with the low dose of Flutiform (100µg/10µg) upon pre-dose FEV<sub>1</sub> were similar to those with the high dose of GSK fluticasone propionate 500µg (alone or in combination with formoterol fumarate 24µg).

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 FEV<sub>1</sub> (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 FEV<sub>1</sub> 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 $\beta_2$ agonist**

Of the five pivotal studies submitted with these Marketing Authorisation Applications three studies were designed such that they facilitate a rigorous, internally validated examination as to whether the long-acting  $\beta_2$  agonist formoterol fumarate “masks” deficient corticosteroid effects of Flutiform upon pre-dose FEV<sub>1</sub>. This endpoint (i.e. change in FEV<sub>1</sub> 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 FEV<sub>1</sub> data in the three specified studies demonstrated that in two of the three studies formoterol fumarate has no effect upon pre-dose FEV<sub>1</sub> whilst in the third study there was some residual formoterol effect upon pre-dose FEV<sub>1</sub> but it was insufficient to explain the magnitude of the pre-dose FEV<sub>1</sub> 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 FEV<sub>1</sub> 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  $\beta$ -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  $\beta_2$  agonist) treatments (Flutiform 500 $\mu$ g/20 $\mu$ g and fluticasone propionate 500 $\mu$ g + formoterol fumarate 24 $\mu$ g) from low dose ICS-LABA treatment (fluticasone propionate 100 $\mu$ g/10 $\mu$ g)

and fluticasone propionate 500µg monotherapy. An annual exacerbation rate ratio of 0.98, i.e. very close to unity for the comparison of Flutiform 500µg/20µg versus fluticasone propionate 500µg + formoterol fumarate 24µg 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> data and their predictive value.

In its recent Consensus Statement on Asthma Control and Exacerbations the ATS/ERS identified pre-dose FEV<sub>1</sub> 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 FEV<sub>1</sub> over both the medium- and longer-term. The Applicant’s own short- and long-term studies have demonstrated the same association between FEV<sub>1</sub> and future exacerbation risk.

In addition to the above is the observation from several published studies that FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub>, given the static nature of FEV<sub>1</sub> after 8 to 12 weeks of treatment, and given the pattern of the FEV<sub>1</sub> 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.

### **2.3. Recommendation**

Having considered the overall submitted data provided by the Applicant in writing and during the oral explanation, the CHMP concluded that the benefit-risk balance of Flutiform 50/5, 125/5 & 250/10 micrograms pressurised inhalation, suspension is positive under normal conditions of use.

The CHMP considered that all concerns raised by the objecting member state to be adequately addressed and that they should not prevent the authorisation of the product.

Therefore, the CHMP recommended the granting of the marketing authorisation for Flutiform 50/5, 125/5 & 250/10 micrograms pressurised inhalation, suspension.

### **2.4. Conclusions and benefit risk assessment**

Based on:

- the results from the studies provided by the applicant
- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the benefit-risk balance of Flutiform and associated names in the applied indications is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure.

**Appendix 1**

*Divergent positions*

## **Article 29(4) referral of Council Directive 2001/83/EC, as amended**

Flutiform and associated names (INN: Fluticasone propionate/Formoterol fumarate)

Procedure No: EMEA/H/A-29/1326

### **Divergent statement**

In the light of the available pharmacokinetic data showing a lower systemic exposure of fluticasone propionate component of this fixed dose combination product, there is a concern that patient receiving the fixed dose combination, whether for the substitution indication or for the step up indication, may not experience the same level of efficacy in respect to long term asthma control.

We are of the opinion that:

The clinical studies did not demonstrate therapeutic equivalence regarding the anti-inflammatory component for this indication.

- PK demonstrated a bioavailability of 67% of fluticasone
- The FEV1 was measured 12 h after the last inhalation, when formoterol still has a bronchodilatory effect, even after long term treatment.
- Clinical symptoms are not sensitive to demonstrate differences in symptomatic asthma control by different doses of ICS, due to the bronchodilatory effects of the concomitant use of long acting  $\beta$ 2 agonists. The studies are also too short to be sensitive.
- No clear head-to-head comparison with current comparators regarding the exacerbation rate has been provided. The demonstrated results are reassuring, but not confirmative.

The long term effects of a possible lower dose ICS combination with LABA are not known, but with the current knowledge concerns are raised regarding the long term safety and adequate long term control of asthma disease.

### **CHMP members expressing a divergent opinion:**

|                          |               |            |
|--------------------------|---------------|------------|
| Daniela Melchiorri       | 19 April 2012 | Signature: |
| Pierre Demolis           | 19 April 2012 | Signature: |
| Arantxa Sancho-Lopez     | 19 April 2012 | Signature: |
| Barbara van Zwieten-Boot | 19 April 2012 | Signature: |

|                 |               |            |
|-----------------|---------------|------------|
| Sol Ruiz        | 19 April 2012 | Signature: |
| Agnes Gyurasics | 19 April 2012 | Signature: |