Public Summary Document

Product: Fluticasone propionate with eformoterol fumarate, inhalation pressurised, 50 micrograms-5 micrograms per actuation, 125 micrograms-5 micrograms per actuation, 250 micrograms-10 micrograms per actuation, 120 actuations, Flutiform®
Sponsor: Mundipharma Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested a Restricted benefit listing for patients who previously had frequent episodes of asthma while receiving treatment with oral corticosteroids and/or optimal doses of inhaled corticosteroids requiring treatment with a combination of and inhaled corticosteroid and a long acting beta-2 agonist.

2. Background

The PBAC has not previously considered this this fixed dose combination inhaled corticosteroid (ICS) with long acting beta agonist (LABA) product.

3. Registration Status

Fluticasone propionate (FP) with eformoterol fumarate (EF) fixed dose combination (FDC), Flutiform®, TGA registered on 14 June 2013 for:
Regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting beta-2 agonist) is appropriate. It is appropriate both for patients not adequately controlled with inhaled corticosteroids and inhaled short-acting beta-2 agonist on an "as required" basis, and for patients already adequately controlled on both an inhaled corticosteroid and a long acting beta-2 agonist.

4. Listing Requested and PBAC's View

Restricted benefit
Patients who previously had frequent episodes of asthma while receiving treatment with oral corticosteroids and/or optimal doses of inhaled corticosteroids requiring treatment with a combination of an inhaled corticosteroid and a long-acting beta 2 agonist.

The PBAC noted that the requested restriction was not consistent with that for other currently PBS-listed asthma maintenance fixed dose combination corticosteroid (ICS) with long acting beta agonist (LABA) products, in that those patients are not required to be stabilised on concomitant inhaled fluticasone and eformoterol before moving to the fixed dose combination.

The PBAC also noted that the National Asthma Council of Australia (NAC) had advised that its Guidelines Committee is currently revising the Asthma Management Handbook, the national treatment guidelines for asthma. It will be renamed the Australian Asthma Handbook when launched as of the seventh edition due in November 2013. The NAC further advised PBAC that it believes it is no longer necessary for patients to be stabilised on separate LABA and ICS inhalers before commencing combination therapy. The NAC indicated that there are questions about the safety of the use of LABA without ICS and that there is increased risk of this happening when two separate inhalers are prescribed.

The PBAC also noted similar advice from The Thoracic Society of Australia and New Zealand (TSANZ) and Dr Helen Reddel (as Chair of the Science Committee for the Global Initiative for Asthma) with regard to the current restriction requirement for patients to be stabilised on separate LABA and ICS inhalers before commencing the combination.

The PBAC indicated its intention to review the PBS restrictions for all fixed dose combination ICS with LABA medicines with a view to aligning these restrictions with the new NAC treatment guidelines.

5. Clinical Place for the Proposed Therapy

Flutiform® fixed dose combination (FDC) metered dose inhaler (MDI) will provide an alternative treatment for patients with asthma needing combination treatment with ICS and a LABA. The individual components of Flutiform® are already separately available on the PBS, as is its administration device. However, the PBAC noted that the proliferation of FDC options, indications, restrictions, doses, device types and colours had the potential to increase confusion in the use of these products, to the detriment of appropriate use of medicines.

6. Comparator

The submission nominated the following comparators:

1) concomitant use of fluticasone plus eformoterol administered via separate inhalers, and;
2) fluticasone/salmeterol

The PBAC considered that the comparison with the fluticasone with salmeterol MDI, to be the most informative comparison for the requested listing. The Committee agreed that there is patient preference for using either the MDI or DPI device options, and noted that only fluticasone with salmeterol is currently PBS-listed as an MDI presentation.

7. Clinical Trials

The submission is based on:

- Two head-to-head randomised trials comparing fluticasone/eformoterol MDI FDC to concomitant fluticasone MDI plus eformoterol MDI (FLT3503 and FLT3505):
  - FLT3503 was an eight week double-blind trial enrolling 620 patients who were randomised to fluticasone/eformoterol FDC 500/20 mcg twice a day (bd) (n=154), fluticasone 500 mcg + eformoterol 24 mcg bd (n=156), fluticasone/eformoterol FDC 100/10 mcg bd (n=155) or fluticasone 500 mcg (n=155) bd.
  - FLT3505 was a 12 week open-label trial enrolling 210 patients randomised to fluticasone/eformoterol FDC (low dose 100/10 mcg bd or high dose 250/10 mcg bd, n=105) or fluticasone (low dose 100 mcg bd or high dose 250 mcg bd plus concurrent eformoterol 12 mcg bd, n=105).

- Two head-to-head randomised trials comparing fluticasone/eformoterol MDI FDC to fluticasone/salmeterol MDI FDC (FLT3501 and FLT 3502):
  - FLT3501 was a 12 week open-label trial enrolling 228 patients randomised to fluticasone/eformoterol FDC (100/10 mcg or 250/10 mcg bd; n=101) or fluticasone/salmeterol FDC (100/50 mcg or 250/50 mcg bd; n=101).

- FLT3502 was a 12 week open-label trial enrolling 211 paediatric (4-12 years of age) patients randomised to fluticasone/eformoterol FDC 50/5 mcg bd (n=106) or fluticasone/salmeterol FDC 50/25 mcg (n=105). Patients who completed trial FLT3502, regardless of which treatment they were randomised to, were eligible to enrol in the 24 week FLT3502 extension study during which all patients received fluticasone/eformoterol FDC 50/5 mcg bd in order to obtain long term safety data.

The PBAC noted that FLT3502 was conducted in paediatric patients and that the TGA approval is restricted to patients aged 12 years and over, and agreed that this trial is of limited relevance to the listing requested.

The published trials and associated reports presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Flutiform vs. Seretide		
FLT3501 Bodzenta-Lakuaszyk, A et al.	Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: An open-label, randomized study.	BMC Pulmonary Medicine (2011); 11: 28.
FLT3502	An open, randomised, parallel group, multicentre study to compare the efficacy and safety of Flutiform pMDI vs. Seretide® pMDI in paediatric subjects with mild to moderate persistent, reversible asthma.	Report date: 26 November 2008 ClinicalTrials.gov Identifier: NCT00475813 Also available at: http://www.mundipharma-rd.eu/?id=55
Flutiform vs. concomitant fluticasone plus eformoterol		
FLT3503 Bodzenta-Lakuaszyk, A et al.	Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler.	Respiratory Medicine (2011); 105: 674-682.
FLT3505	An open, randomised, parallel group, multicentre study to compare the efficacy and safety of Flutiform pMDI vs. Fluticasone pMDI plus Formoterol DPI in adolescent and adult subjects with mild to moderate-severe persistent, reversible asthma.	Report date: 07 January 2009 ClinicalTrials.gov Identifier: NCT00563056 Also available at: http://www.mundipharma-rd.eu/?id=55
Supplementary safety studies		
FLT3502	An open-label, multicentre extension study to collect safety data on FlutiForm pMDI long-term treatment in paediatric subjects with mild to moderate persistent, reversible asthma.	Report date: 26 November 2008 ClinicalTrials.gov Identifier: NCT00475813 Also available at: http://www.mundipharma-rd.eu/?id=55
SKY-003	Study SKY2028-3-003 Long-term open-label safety study with	Report date: 16 December 2008.

	SKP Flutiform HFA pMDI (100/10 µg and 250/10 µg) in adult and adolescent patients with asthma.	ClinicalTrials.gov Identifier: NCT00394121

8. Results of Trials

The submission claimed that as the lower 95% confidence interval of the pooled mean difference in change in pre-dose FEV_1 from baseline in Trials FLT3501 and FLT3502 is greater than -0.2, the non-inferiority margin is satisfied and that fluticasone/eformoterol FDC is non-inferior to fluticasone/salmeterol FDC in FEV_1 improvement.

The PBAC agreed that the non-inferiority margins used in the submission were reasonable.

The submission also claimed that the non-inferiority of fluticasone/eformoterol FDC to fluticasone and eformoterol given concomitantly is demonstrated in Trial FLT3503 as the lower 95% confidence interval is greater than -0.2. The results from ITT population supports the results from the per protocol population.

The submission stated that as Trial FLT3505 did not record pre-dose FEV_1 at the study endpoint, therefore the mean difference in pre-dose FEV_1 at baseline and post-dose FEV_1 at study endpoint was calculated instead as the outcome. The clinical relevance of comparing post dose FEV_1 after 8-12 weeks of treatment with pre-dose FEV_1 is uncertain.

For PBAC's view of the evidence of comparative effectiveness, see under "Clinical Claim" and "Recommendations and Reasons."

With regard to comparative harms, the PBAC agreed that trial results presented in the submission showed very few adverse events during the trials, and that no statistically significant differences between the treatment groups were found. Adverse event outcomes from Trials FLT3501 and FLT3502 support the non-inferiority claim of fluticasone/eformoterol FDC versus fluticasone/salmeterol FDC and adverse event outcomes from Trials FLT3503 and FLT3505 support the non-inferiority claim of fluticasone/eformoterol FDC versus fluticasone and eformoterol used concurrently.

The PBAC noted that submission provided additional data on potential safety concerns beyond those identified in the clinical trials. Overall, the PBAC considered that there are no safety concerns regarding the fluticasone/eformoterol FDC suggested in the literature.

9. Clinical Claim

The submission described the fluticasone/eformoterol FDC as non-inferior in terms of comparative effectiveness and non-inferior/equivalent in terms of comparative safety compared with fluticasone and eformoterol administered concurrently as well as the fluticasone/salmeterol FDC.

The PBAC considered the comparison with the fluticasone with salmeterol MDI to be the most informative for the requested listing.

The PBAC considered that, for the low and mid strength fluticasone with eformoterol MDI, the clinical trial evidence presented in the submission against fluticasone with salmeterol

MDI, supported a conclusion of non-inferiority in terms of comparative effectiveness and safety.

The PBAC noted that the only clinical trial evidence presented for the high strength 250/10 fluticasone with eformoterol MDI was against the components administered concomitantly. No evidence was presented to demonstrate that this presentation is non-inferior to, or provides a significant improvement in efficacy or reduction in toxicity compared to the high strength 250/25 fluticasone with salmeterol MDI, which PBAC again considered the most informative comparison for the requested listing. However, PBAC considered it reasonable to conclude that the high strength fluticasone with eformoterol MDI would deliver similar clinical outcomes for asthma maintenance to the high strength fluticasone with salmeterol MDI.

10. Economic Analysis

The submission presented a cost-minimisation analysis for the fluticasone with eformoterol MDI based on the sum of the components per actuation.

The PBAC did not accept this approach to pricing the fluticasone with eformoterol MDI *(see Recommendation and Reasons)*.

11. Estimated PBS Usage and Financial Implications

The submission's estimate of the likely number of prescriptions dispensed per year was in the range 100,000 – 200,000 in Year 5, at an estimated net cost per year to the PBS between $10 – 30 million in Year 5.

The PBAC noted that the submission's estimate of a net cost to the PBS is based on the higher prices proposed by the sponsor than those resulting from the PBAC recommendation.

The PBAC also considered that, overall, the submission's estimates of PBS usage are uncertain, with the submission potentially overestimating the proportion of ICS/LABA FDCs being used for asthma, and the submission's assumptions about the proportion of the current market that would be 'available for substitution', and the uptake rates not well justified.

The PBAC agreed that there is potential for the new listing to be used for Single Maintenance and Reliever Therapy (SMART) and for chronic obstructive airway disease (COPD) due to the common eformoterol component. The PBAC noted that the current subsidy prices for the for reliever component of SMART and for COPD are lower than the current subsidy price for asthma maintenance. Although acknowledging the sponsor's commitment to not promote the fluticasone/eformoterol MDI for SMART or COPD, the Committee nonetheless considered that the risk of use in these indications had financial implications for Government that should also be managed through pricing and/or risk share arrangements.

12. Recommendation and Reasons

The PBAC recommended the listing of fluticasone with eformoterol pressurised metered dose inhalers (MDI) for maintenance treatment of asthma on a cost-minimisation basis with fluticasone with salmeterol pressurised MDI. The PBAC accepted the following equi-effective doses for asthma maintenance for the purposes of cost minimisation:

- fluticasone propionate 50 mcg with eformoterol fumarate 5 mcg MDI, 2 actuations twice daily is equivalent to fluticasone propionate 50 mcg with salmeterol 25 mcg MDI, 2 actuations twice daily;
- fluticasone propionate 125 mcg with eformoterol fumarate 5 mcg MDI, 2 actuations twice daily is equivalent to fluticasone propionate 125 mcg with salmeterol 5 mcg MDI, 2 actuations twice daily; and
- fluticasone propionate 250 mcg with eformoterol fumarate 10 mcg MDI, 2 actuations twice daily is equivalent to fluticasone propionate 250 mcg with salmeterol 25 mcg, 2 actuations twice daily.

The PBAC considered that, for the low and mid strength fluticasone with eformoterol MDI, these equi-effective doses are consistent with the clinical trial evidence presented in the submission against the fluticasone with salmeterol MDI, which PBAC considered the most informative comparison for the requested listing.

The PBAC did not accept the submission's proposal to price the new fluticasone with eformoterol MDI be based on the sum of the components per actuation. This method does not take account of the difference in the number of actuations in a standard dose of the proposed MDI versus the eformoterol DPI (MDI 2 vs DPI 1). As a result, the proposed prices for one month's treatment with the fluticasone/eformoterol MDI (50/5, 125/5, 250/10 x 30 days at 2 actuations twice daily) combine the cost of one month's treatment with equivalent per dose amounts of fluticasone MDI (50/125/250 mcg x 30 days at 2 actuations twice daily) with two months treatment with the closest per dose amount of eformoterol DPI (6/12 mcg x 60 days at 1 actuation twice daily).

The Committee noted that if the prices for the low and mid strength fluticasone/ eformoterol MDI are calculated by combining the cost of one month's treatment with fluticasone 50 or 125 mcg x 2 actuations twice daily with one month's treatment of eformoterol 12 mcg x 1 actuation twice daily, then the resultant prices for these two presentations are similar to the prices calculated on the basis of the equi-effectiveness with fluticasone/salmeterol MDI recommended by PBAC. However, the Committee did not consider this alternative method appropriate for pricing the high dose 250/10 presentation of fluticasone/eformoterol because it results in prices that are higher than those for the high dose fluticasone/salmeterol MDI, which would be inconsistent with its aforementioned conclusion that the high strength fluticasone/eformoterol MDI is likely to deliver similar clinical outcomes for asthma maintenance to the high strength fluticasone/salmeterol MDI.

Lastly, the PBAC noted that the restriction wording proposed by the sponsor differs from that for other currently PBS-listed asthma maintenance fixed dose combination corticosteroid (ICS) with long acting beta agonist (LABA) products. The difference is that the proposed new listing allows patients whose asthma remains uncontrolled to move directly from (any) oral or ICS to the fixed dose combination MDI rather than requiring them to be stabilised on concomitant inhaled fluticasone and eformoterol.

In this context, the PBAC also noted the NAC concerns about the safety of the use of LABA without ICS and there is risk of this happening when two separate inhalers are prescribed. The PBAC indicated its intention to review the PBS restrictions for all fixed dose combination ICS with LABA medicines with a view to aligning these restrictions with the new NAC treatment guidelines. Other issues to consider in this review include whether to

specify a class of medicine or the component medicine in these restrictions and whether any age restrictions should apply. The Committee requested its Secretariat request the input of sponsors of PBS subsidised ICS with LABA combinations and other relevant stakeholders prior to PBAC considering this issue further.

The PBAC recommended that fluticasone with eformoterol pressurised metered dose inhaler is suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

Outcome:
Recommended

Recommended listing

Add the following new items

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name an Manufacturer
FLUTICASONE PROPRIONATE WITH EFORMOTEROL FUMARATE			
Powder for inhalation 50 micrograms – 5 micrograms per actuation (120 actuations)	1	5	Flutiform 50/5 MF
Powder for inhalation 125 micrograms – 5 micrograms per actuation (120 actuations)	1	5	Flutiform 125/5 MF
Powder for inhalation 250 micrograms – 10 micrograms per actuation (120 actuations)	1	5	Flutiform 250/10 MF

Condition/Indication:	Asthma
Restriction:	Restricted Benefit *Restriction to be finalised*

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The Sponsor welcomes the PBACs decision and will be working towards ensuring that patients have access to a broader choice of treatments to control their asthma.