10 April 2013
EMA/210436/2013

Assessment report for Kantos Master and associated names

INN/active substance: beclometasone dipropionate, formoterol fumarate

Procedure number: EMEA/H/A-13/1350

Referral under Article 13(2) of Commission Regulation EC No 1234/2008

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

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 23 December 2011, Chiesi Farmaceutici S.p.A submitted an application for Kantos Master and associated names through a mutual recognition procedure (MRP) type II variation (DE/H/0873/001/II/024) with Germany acting as Reference Member State (RMS). The Concerned Member State (CMS) were: Austria, Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.
The Marketing Authorisation for the medicinal product Kantos Master and associated names has been withdrawn in Portugal on 24 July 2012 following Marketing Authorisation Holder request (MAH), and the Marketing Authorisation has ceased to be valid in Slovakia due to the sunset clause.

The applied variation was to include: “Maintenance and reliever therapy taken as regular maintenance treatment and as needed in response to asthma symptoms”.

The type II variation procedure started on 20 January 2012. Since no agreement was reached between the RMS and the CMS the procedure was referred to CMD(h) by Germany on 08 July 2012. The CMD(h) 60 day procedure was initiated on 24 September 2012.

Day 60 of the CMD(h) procedure was on 22 November 2012, and since there could be no agreement the procedure was referred to CHMP.

On 23 November 2012, Germany triggered a referral under Article 13 of Commission Regulation EC No 1234/2008. The CHMP was requested to give its opinion on whether the variation for medicinal products containing Kantos Master and associated names should be granted or refused.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

Kantos Master is a fixed-dose combination (FDC) of the inhaled corticosteroid (ICS) beclometasone dipropionate (BDP) and the long-acting beta$_2$-agonist (LABA) formoterol fumarate (FF). BDP is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone-17-monopropionate (B17MP) which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate. Formoterol is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1 to 3 minutes after inhalation, and has a duration of 12 hours after dose administration.

The medicinal product Kantos Master is a solution delivered through a pressurised metered dose inhaler (pMDI). The active ingredients have an high “extra-fine” particle fraction (i.e. mass median aerodynamic diameter MMDA around 1.5µm or less), enabling efficient lung distribution and deposition through the entire bronchial tree, while minimising systemic exposure through reduced gastrointestinal absorption.

Kantos Master is currently indicated as regular maintenance treatment of asthma administered twice daily, with once-daily treatment as an option when down-titrating to the lowest effective dose. For relief symptoms, patients are advised to have a separate short-acting beta$_2$-agonist (SABA).

Using a different approach for asthma management, a maintenance dose of a fixed combination of ICS and LABA and additional doses of the same combination in case of symptom worsening may be used instead of a separate SABA. This approach for asthma management is called “Maintenance And

Reliever Therapy" (MART). The MART approach is to reduce the rate of asthma exacerbations by "early intervention", i.e. by giving additional doses of ICS plus FF in response to an increase in symptoms (2011 GINA Guidelines[1]).

In this variation application the MAHs applied for Kantos Master to be used in patients with persistent asthma as regular maintenance treatment and as needed is response to symptoms, in addition to the currently approved indication as maintenance treatment only.

On the basis of the questions raised by Sweden the points to be considered by the CHMP were:

1. The data from the main pivotal study that were submitted with the application to support safety and efficacy of Kantos Master for the maintenance and reliever therapy taken as regular maintenance treatment and as needed in response to asthma symptoms have not demonstrated that the MART treatment regimen was non-inferior to standard of care treatment, as the control group did not actually receive treatment according to standard of care.

2. The extrapolation of data from Symbicort SMART was questionable as the similarity of these two products in the MART regimen has not been established.

2.2. Clinical efficacy

In order to demonstrate efficacy and safety of Kantos Master and associated names as maintenance treatment and as needed in response to symptoms of asthma, the application dossier was based on one pivotal clinical study (CT07) and three supportive studies (CT06, CP03 and HS1). The supportive studies will not be discussed as the referral procedure was initiated due to a disagreement in the main clinical study (CT07).

The pivotal phase III clinical study (Study CT07) was conducted to demonstrate efficacy of Kantos Master and associated names as maintenance treatment and as needed in response to worsening of asthma symptoms. This was a 48 weeks, randomised, double-blind, double dummy, two arms parallel group study comparing the efficacy of Kantos Master (100µg BDP/6µg FF) given both as maintenance and reliever versus Kantos Master given as maintenance plus SABA (100µg salbutamol) given as reliever in partially controlled or uncontrolled asthmatics.

This study was designed as a superiority study with time to first severe asthma exacerbation as primary variable. Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment, or resulting in the need for systemic steroids (e.g. oral, intramuscular or intravenous steroids) for more than three days.

The secondary efficacy variables were:

- Asthma Control Questionnaire (ACQ) score (at all visits from Screening)
- Peak Expiratory Flow (PEF) (morning and evening PEF and daily variability)
- Forced Expiratory Volume in the 1st second (FEV_1), Forced Vital Capacity (FVC), Forced Expiratory Flow ($FEF_{25-75\%}$)(pre-dose at all visits from Screening)
- Total asthma symptom scores (recorded daily)

Patients enrolled in the study were partially controlled or uncontrolled asthmatics (according to *Global Initiative for Asthma [GINA] guidelines, 2007*[2]) and were being treated with low-medium doses of ICS

[1] *Global Strategy for Asthma Management and Prevention*, Global Initiative for Asthma (GINA) 2011. Available from: http://www.ginasthma.org/.

[2] *Global Strategy for Asthma Management and Prevention*, Global Initiative for Asthma (GINA) 2007. Available from: http://www.ginasthma.org/.

as monotherapy (total daily dose ≥ 1000µg non-extrafine BDP or equivalent) or ICS in a fixed combination with LABA (total ICS daily dose ≥ 500µg non-extrafine BDP or equivalent) at a constant dose for two months before the first visit. The patients eligible had a FEV_1 > 60% of the predicted normal value, with a mean FEV_1 % of predictive normal value of 74-75%.

A total of 1714 patients were randomised to receive the assigned reliever treatment, in addition to the maintenance treatment with Kantos Master. 857 patients were randomised to receive Kantos Master as reliever medication (Kantos group) and 857 were randomised to receive salbutamol as reliever medication (salbutamol group) (99 patients in the Kantos group and 109 patients in the salbutamol group, were withdrawn from the study after randomisation).

2.2.1. Results

Study CT07

The analysis of the primary efficacy variable showed that Kantos Master as reliever medication significantly prolonged the time to first severe asthma exacerbation compared to salbutamol (p<0.001). The risk of experiencing a severe asthma exacerbation was reduced by 36% (CI: 18% - 51%) in the group taking Kantos Master (Kantos group) as reliever compared to the group taking salbutamol (salbutamol group), and the difference between groups was statically significant (p<0.001). Moreover, the rate of severe asthma exacerbations was significantly lower in the Kantos group than in the salbutamol group (p<0.001).

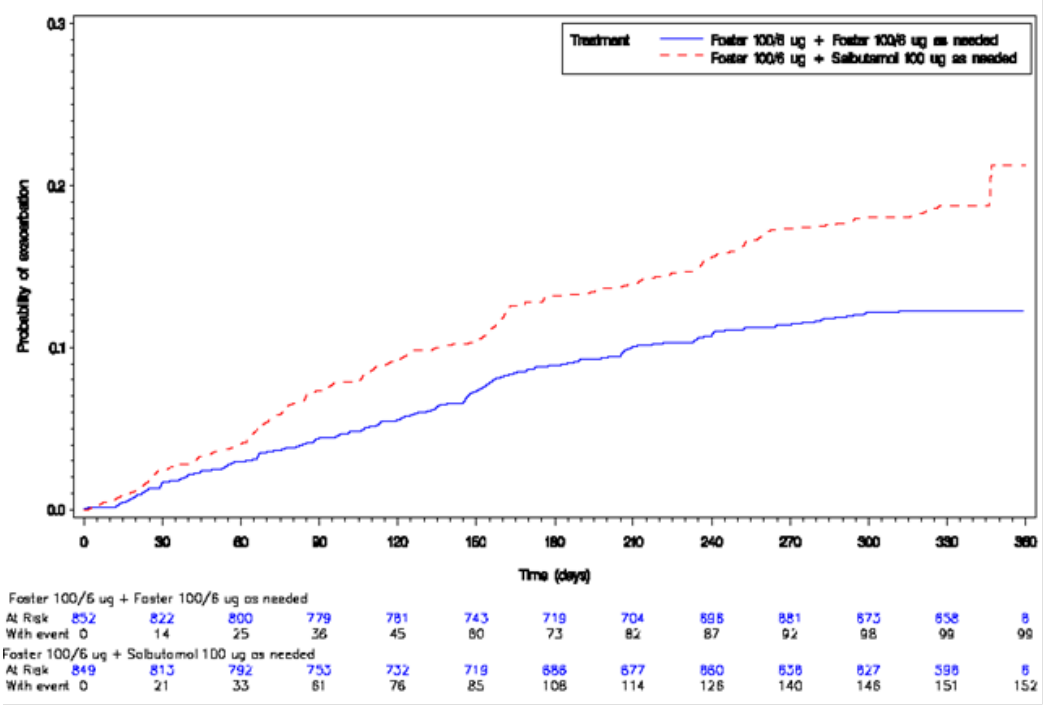

Figure 1: Kaplan-Meier estimate of the time to first severe asthma exacerbation (ITT population, Study CT07)

The analysis of the secondary efficacy variables (FEV_1, asthma symptom, rescue use etc) showed a clear improvement in both treatment arms, indicating the effectiveness of the maintenance therapy with Kantos Master one inhalation twice a day in these patients. The mean FEV_1 improved in both

groups of patients during the run-in period with a change from baseline to the end of the study of about 100 mL in both groups (Figure 2).

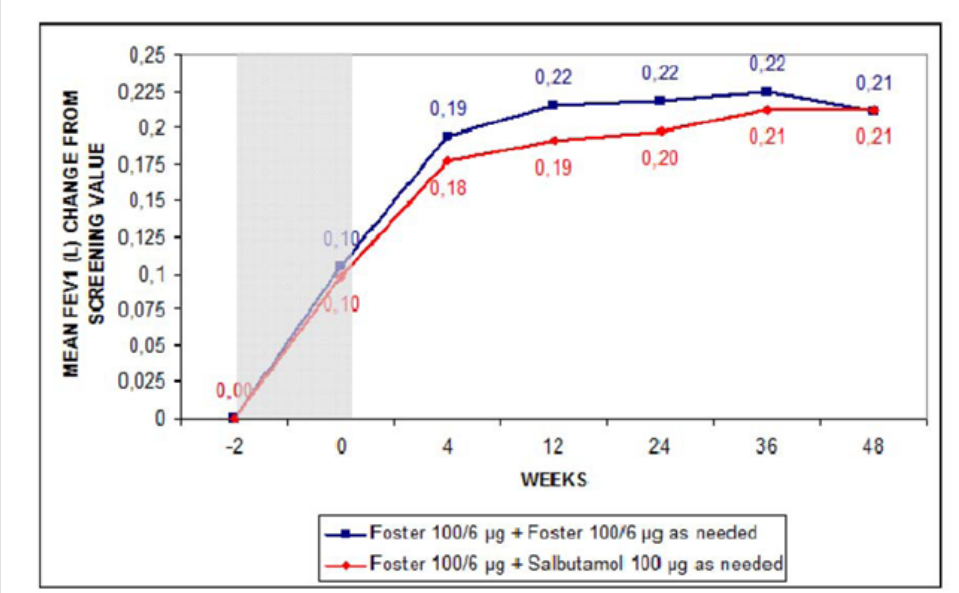

Figure 2: Mean pre-dose FEV1 changes from screening to the end of treatment

The improvement in asthma control was mirrored by a reduction of use of reliever medication and other parameters (medication free days, asthma symptom scores, asthma symptom free days) in both groups, suggesting that the ICS-LABA maintenance therapy was adequate to control both lung function and symptoms.

2.2.2. Discussion

Study CT07

The patients enrolled in the clinical study CT07 were being treated with a higher mean ICS dose at entry to the study (between 700µg and 1100µg, expressed as labelled or BDP equivalent dose respectively) than during the clinical study (mean ICS dose in Kantos group and in salbutamol group was respectively about 701.2 µg/day and 488.8 µg/day, always given as part of an ICS-LABA combination). Although a reduction to the mean ICS dose was observed in patients at entry to the study, the results showed that the mean FEV_1 improved in both groups of patients during the run-in period and further improvement were observed during the 48-week treatment period, with a change from baseline to the end of the study of about 100mL in both groups. Significant and comparable improvements from baseline were also observed for the ACQ score (decrease), in the percentage of asthma symptom-free days and asthma controls days (increase) in both treatment arms over the course of one year treatment, even in the group of patients not taking additional ICS dose as rescue. It was considered that these results could have not been observed in both arms if the patients were undertreated. The CHMP noted that there was no comparison with the standard of care, according to the GINA guideline. However, the CHMP agreed that there was no evidence that patients in the comparator group were under-treated as patients in both group had shown clinical benefit from their maintenance treatment.

The daily maintenance dose, in both arms of the study was 200µg of extrafine beclometasone, which is clinically equivalent to 500µg of non extrafine beclometasone. It was also observed that the group of patients using Kantos Master as reliever took on average approximately 80µg more of BDP per day which is equivalent to less than one extra inhaler actuation per day. However, it has never been

demonstrated that a small increase in total ICS dose would have an impact on the lung function or on the clinical outcomes.

Therefore, it was concluded that the positive effect on exacerbations was not achieved through a simple increase in daily ICS dose but with the timely delivery of a small dose of BDP together with the bronchodilator, when patient's symptoms worsened. The key factor of the MART approach is not the overall amount of ICS given, but when the dose is given. The concept of this "early intervention" is clearly advocated in the 2011 GINA guidelines[1] where it is stated that "The benefit in preventing exacerbations appears to be the consequence of early intervention at a very early stage of a threatened exacerbation".

To further demonstrate that the patients in the MART treatment arm were not overtreated or undertreated and to support the results of the study CT07, the MAH conducted post hoc analysis of data and made reference to additional supportive data.

Post hoc analysis of data from study CT07

The post hoc analysis was conducted on the same primary endpoint that the study CT07, which was time to first severe exacerbation, as well as on the overall number of severe exacerbations.

Two subgroups of patients were considered: one arm received an entry ICS dose of 500µg or less and another arm received an entry ICS dose of more than 500µg.

The results demonstrated that MART is significantly superior to salbutamol in prolonging the time to first severe exacerbations and in reducing the mean yearly rate of severe exacerbations in both subgroups of patients. The primary endpoint is a clinically important measure of the long-term asthma control, and was clearly in favour of Kantos MART in comparison with Kantos plus SABA treatment.

Analysis on Severe Exacerbations
First Severe Exacerbation and Overall Number of Severe Exacerbations
INTENT-TO-TREAT POPULATION

	ICS dose at study entry < =500 mcg BDP NE		ICS dose at study entry > 500 mcg BDP NE	
	CHF1535 100/6 N=141	Salbutamol N=140	CHF1535 100/6 N=711	Salbutamol N=709
TIME TO FIRST EXACERBATION				
Number of patients with at least one exacerbation	8	24	91	128
Probability to develop one exacerbation in 48 weeks	6.27%	18.20%	13.40%	21.52%
Log-rank test (p-value)	7.2288 (0.0072)		7.6062 (0.0058)	
Hazard ratio (95% CI) from Cox Model	0.331 (0.148, 0.738)		0.688 (0.526, 0.900)	
OVERALL NUMBER				
Total number of severe asthma exacerbations	12	31	118	165
Mean rate per 100 patients per year	10.27	26.31	18.99	26.84
Mean Rate per 100 patients per year from Poisson model	8.23	21.36	16.12	22.70
Rate ratio (95% CI) CHF1535 100/6 vs. Salbutamol	0.385 (0.219, 0.679)		0.710 (0.581, 0.868)	
p-value	0.001		0.0008	

Table 1: Post-hoc analysis on Severe Exacerbations in study CT07

Therefore, it was considered that the positive therapeutic effect of MART with Kantos Master has been demonstrated in patients who had a reduction in the daily ICS dose and in patients who did not have any step down treatment (i.e. the subgroup of patients taking up to 500µg daily at entry and during treatment). The CHMP was therefore of the opinion that the effectiveness of MART was not due to a potential under-treatment of the comparator arm in the study CT07.

A further additional analysis of the study CT07 has been conducted in patients with severe asthma as it was considered that if under-treatment with Kantos Master in MART occurred, it should be most evident in this population who requires higher ICS doses to control their asthma. The disease severity was based on lung function (FEV_1) and use of rescue medication at entry to the study. In both more severe (defined by FEV_1 < 70%) and less severe groups (FEV_1 ≥ 70%), Kantos Master in MART was

significantly efficacious (similar hazard ratio of 0.65 and 0.61, respectively). Kantos Master in MART was also significantly efficacious regarding the mean number of rescue medication at entry to the study (>0 and ≤1, >1 and ≤2, and >2) in the three groups (similar hazard ratio of 0.51, 0.64 and 0.52, respectively). This additional analysis further demonstrated that Kantos Master in MART is not associated with under-treatment of patients in case of uncontrolled asthma

The CHMP concluded that the effectiveness of MART was not due to a potential under-treatment of the comparator arm in the study CT07, and that the maintenance administration of Kantos Master at 1 inhalation twice a day had a clinically significant benefit in these patients.

Additional supportive data

Literature data

In addition to the data from the pivotal clinical study CT07, the CHMP took note of literature data where the principle of MART is substantiated with the use of an ICS and LABA. The data in the literature suggested that dose reduction from high to moderate maintenance ICS does not affect outcomes of MART treatment. For instance, in the SMILE study[3], the dose of budesonide (400µg/day) was in line with the ICS dose administrated in the study CT07 (500µg BDP non-extrafine equivalent). This comparability has also been confirmed in a comparative clinical study between Kantos Master and associated names (Foster 100/6) and Symbicort 200/6 (budesonide/formoterol)[4]. In addition, in the Symbicort MART development program, marked improvements in asthma control have been obtained when part of the dose was given on an as-needed basis. These results were irrespective of the type of fixed ICS/LABA comparator (budesonide/formoterol or salmeterol/fluticasone), and irrespective of whether the maintenance dose of the comparator was similar or up to two fold higher. As a consequence, these results showed that the dose reduction of ICS and the type of fixed ICS/LABA comparator does not affect the outcome of the treatment.

The CHMP also took into account the suitability of Kantos Master (in terms of its components and its formulation) for the MART approach. Both components (BDP and FF) have been shown to be effective in the case of asthma exacerbation due to their anti-inflammatory and bronchodilating effects, and their effects are enhanced if they are administered in combination. In addition, both components have been developed as an extrafine formulation, which means they reach the most peripheral airways where most of the inflammatory process takes place during asthma exacerbation. The similar particle size of the two components also leads to co-deposition in the same regions of the lung, favouring a synergistic interaction. Moreover, the onset of action of formoterol as a bronchodilator is faster compared to other LABAs such as salmeterol, and is therefore well suited for the acute relief of bronchospasm.

Furthermore, in a previous published study (Papi et al. 2007[5]) Kantos and Symbicort have been compared. When used as maintenance treatment in moderate-to-severe asthmatic patients over a 3-month period, they produced equivalent benefits in terms of lung function, clinical symptoms, rates of asthma exacerbation, and use of rescue medications. Therefore, a similar effect of KANTOS compared to Symbicort in relieving symptoms and reducing severe asthma exacerbations can be expected when given as maintenance and reliever therapy.

[3] Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006; 368:744–753.
[4] Fabbri L.M. Inhaled beclometasone dipropionate /formoterol extra fine fixed combination in the treatment of asthma: evidence and future perspectives. Expert Opinion Pharmacother. (2008) 9(3).
[5] Papi et al. Beclomethasone/formoterol vs budesonide/formoterol combination therapy in asthma. Eur.Resp.J.2007; 29: 682-689

2.3. Overall benefit/risk assessment

In view of the data submitted, the CHMP agreed that study CT07 indicated a significant reduction in the risk of severe exacerbations of asthma and significant longer time to exacerbation can be obtained when part of Kantos Master dose is given as needed.

The CHMP noted that there was no comparison with the standard of care, according to the GINA guideline. However, the CHMP was of the opinion that the effectiveness of MART was not due to a potential under-treatment of the comparator arm in the Study CT07 as both groups had shown clinical benefit from their maintenance treatment. In addition, the CHMP took note of literature data where the principle of MART is substantiated with the use of and ICS and LABA. As Kantos Master contain formoterol and beclometasone, and in view of the results of the study, the CHMP considered the published data to be relevant in the applied regimen.

In conclusion, the CHMP considered that the benefit/risk of Kantos Master and associated names for the maintenance and reliever therapy taken as regular maintenance treatment and as needed in response to asthma symptoms is positive and therefore recommended the variation to the term of the marketing authorisations.

2.4. Changes to the product information

The Summary of Product Characteristics, Labelling and Package Leaflet remain as per the final versions agreed during the Coordination Group procedure.

3. Overall conclusion

- The Committee considered the referral under article 13 of Regulation No 1234/2008
- The Committee reviewed all available data submitted by the MAH, to support the safety and efficacy of Kantos Master and associated names for “maintenance and reliever therapy taken as regular maintenance treatment and as needed in response to asthma symptoms”.
- The Committee is of the opinion that the data of the pivotal study CT07 indicated a significant reduction in the risk of severe exacerbations of asthma and significant longer time to exacerbation can be obtained when Kantos Master dose is given as needed.
- The Committee noted that there was no comparison with the standard of care, according to the GINA guideline. However, the Committee agreed that there was no evidence that patients in the comparator group were under-treated as patients in both group had shown clinical benefit from their maintenance treatment.
- The Committee took note of literature data where the principle of MART is substantiated with the use of an ICS and LABA. As Kantos Master contain formoterol and beclometasone and in view of the results of the study, the Committee considered the published data to be relevant in the applied regimen.
- The Committee concluded, in view of available data that the benefit/risk of Kantos Master and associated names for “maintenance and reliever therapy taken as regular maintenance treatment and as needed in response to asthma symptoms” is positive.

Therefore, the CHMP recommended the granting of the variation to the terms of the marketing authorisations for the medicinal products referred to in Annex I for which the valid 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.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.