Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Scientific conclusions

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

Background

Kantos Master is a fixed-dose combination (FDC) of the inhaled corticosteroid (ICS) beclometasone diproprionate (BDP) and the long-acting beta$_2$-agonist (LABA) formoterol fumarate (FF) which is indicated as regular maintenance treatment of asthma administrated twice daily. Kantos Master has received marketing authorisation in the European Union through the Mutual Recognition Procedure (MRP).

On 20 January 2012, the MAH submitted a type II variation via the MRP for Kantos Master and associated names (DE/H/0873/001/II/024), to request the inclusion of "Maintenance and reliever therapy taken as regular maintenance treatment and as needed in response to asthma symptoms".

As the reference and concerned Member States were not able to reach an agreement in respect of the variation, on 23 November 2012, Germany triggered a referral under Article 13 of Commission Regulation EC No 1234/2008.

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.

The referral procedure was initiated on 13 December 2012.

Scientific discussion

Study CT07

In order to demonstrate the efficacy of Kantos Master and associated names as maintenance treatment and as needed in response to symptoms of asthma, the MAH submitted data from a phase III pivotal clinical study, randomised, double blind, double dummy, two arms parallel group (Study CT07).

This treatment approach of using a maintenance dose of a fixed combination of ICS and LABA and additional doses of the same combination in case of symptom worsening instead of a separate short acting beta$_2$-agonist (SABA) is called "Maintenance And Reliever Therapy" (MART). The aim of 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]).

The study CT07 compared the efficacy of Kantos Master and associated names given as both maintenance and reliever therapy and Kantos Master given as maintenance therapy with salbutamol (short acting beta$_2$ -agonist SABA) as reliever therapy in partially controlled or uncontrolled asthmatics, over a 48 weeks treatment.

The results of the study have shown that the risk of experiencing a severe asthma exacerbation was reduced by 36% (CI: 18% - 51%) in the group taking Kantos Master as reliever compared to the

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

group taking salbutamol, and the difference between groups was statistically significant ($p<0.001$). Significant improvements were also observed in the secondary efficacy variables (Forced Expiratory Volume in the 1st second (FEV1), asthma symptoms, medication free days etc.) in both treatment arms. This suggested that the ICS-LABA maintenance therapy was adequate to control both lung function and symptoms.

The patients enrolled in this study 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 (ICS dose in the group taking Kantos Master as reliever and in the group taking salbutamol 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. 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, the CHMP was of the opinion that the positive effect of Kantos Master 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. It was concluded that 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

A post hoc analysis was conducted with two subgroups of patients in order to demonstrate that both groups of patients in the study CT07 were not overtreated or undertreated. One arm of patients were treated with an entry ICS dose of 500 µg or less and another arm had an entry ICS dose of more than 500 µg. The results demonstrated that MART with Kantos Master was 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. Therefore, the CHMP 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 500 µg daily at entry and during treatment).

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 was therefore of the opinion that the effectiveness of Kantos Master in 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 one inhalation twice daily had a clinically significant benefit in these patients.

Additional supportive data

Literature data

Further evidence in the literature has suggested that dose reduction from high to moderate maintenance ICS does not affect outcomes of MART treatment. For instance, in the SMILE study[2], 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 10/6) and Symbicort 200/6 (budesonide/formoterol)[3]. 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.

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.

Conclusion

The CHMP considered that the data provided by the MAH are sufficient to support the use of Kantos Master and associated names in the maintenance and reliever therapy (MART) taken as regular maintenance treatment and as needed in response to asthma symptom. The CHMP also 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 submitted study, the Committee considered the published data to be relevant in the applied regimen.

[2] 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.
[3] 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).

Grounds for the variation to the terms of the marketing authorisations

Whereas

- The Committee considered the referral under article 13(2) of Regulation No 1234/2008
- The Committee reviewed all available data, 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.