Annex II

Scientific conclusions

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The applicant Sun Pharmaceuticals has submitted an application in accordance with Article 10(3) of Directive 2001/83/EC under the decentralised procedure for Budesonide SUN 250 microgram/2 ml nebuliser suspension, Budesonide SUN 500 microgram/2 ml nebuliser suspension, Budesonide SUN 1000 microgram/2 ml nebuliser suspension and associated names (NL/H/4194/001-003/DC). The reference medicinal product for this application is Pulmicort Respules (250 microgram /2 ml, 500 microgram /2 ml, 1000 microgram /2 ml) registered by AstraZeneca. Budesonide nebuliser suspension, which is a glucocorticosteroid with a high local anti-inflammatory action, is an inhalation medicinal product consisting of a nebuliser suspension containing the active substance in insoluble form.

The applicant has applied for the below indications:

- adults and children, in particular children aged 4 years and above, with bronchial asthma, who should be treated with corticosteroids and for whom other local dosage forms are unsatisfactory or inappropriate
- children aged 6 months to 4 years with recurrent or persistent complaints of coughing and/or wheezing, in whom a diagnosis of asthma is suspected.
- very serious pseudocroup (Laryngitis subglottica) in which hospitalisation is indicated.

The grounds of the referral procedure were disagreements with regards to which *in-vitro* data are considered pivotal for the assessment of the equivalence of the reference and the test product for this application.

The *CHMP Guideline on the requirements for clinical documentation for orally inhaled products (OIP)* (CPMP/EWP/4151/00 Rev.1), referred as 'OIP equivalence guidance' hereafter, provides in Section 4.3 that: *"For suspensions for nebulisation therapeutic equivalence should be demonstrated through in-vivo studies, unless justification is provided for the use of other types of studies to demonstrate equivalence."* and in Section 5.2 that *"For abridged applications therapeutic equivalence to a reference medicinal product must be substantiated. In some cases, the use of only comparative in vitro data, obtained with an accepted method (e.g. multistage impactor/impinger), may be considered acceptable if the product satisfies all of the following criteria (compared with the reference product)".*

The criteria to substantiate equivalence include: active substance, identical dosage form, active substance in the solid state, qualitative and/or quantitative differences in excipients should not influence the performance of the product and should not change its safety profile, similar target delivered dose should be similar (within +/- 15%) and aerodynamic particle size distribution (APSD) comparisons of the test/reference ratio (T/R) should be within +/- 15% (CI 90%), with at least 4 groups of stages. Justification should be based on the expected deposition sites in the lungs.

On the basis of the OIP equivalence guidance, the applicant did not conduct any clinical studies to support the application and instead provided the results of *in-vitro* tests.

All the requirements of the guidance were met apart from the requirement of the aerodynamic performance of the test as compared to the reference product performed per impactor stage or justified group of stages. All strengths were tested and differences were observed for some grouped stages of the APSD comparison as the T/R ratio 90% confidence intervals fell outside the pre-defined maximum allowed range of variability of +/- 15% (85, 117.65).

To justify the observed difference, the applicant provided an extensive characterisation of the test and reference product. All the *in-vitro* tests performed with the test and reference product as suspension for nebulisation prior to nebulisation demonstrated that the nebuliser suspensions have equivalent

chemical and physical characteristics, such as the same critical quality attributes (CQA) that might have an impact on the dissolution and absorption of the active substance in the lung (including density, viscosity, surface tension, resuspendability, sedimentation rate, pH, osmolality and particle size distribution [PSD] of the suspended particles).

Two Concerned Member States (CMS), namely the UK and Italy, considered that therapeutic equivalence of the products has not been demonstrated for the following reasons:

- With regards the PSD in the suspension for nebulisation before nebulisation, it was considered that the data and information provided for the used method (Morphology G31D) is not adequate to demonstrate equivalence of the test and reference product.

- The APSD comparison between test and reference, which is considered as a CQA, fell outside the maximum allowable pre-defined variability range of 85.00-117.65% and therefore the OIP equivalence guidance criteria are not fulfilled, thus the equivalence has not been demonstrated.

- Furthermore, it was considered that the justifications provided for the observed differences for the APSD results are not acceptable and that the arguments and data provided may raise additional concerns related to the quality of the test product.

Overall summary of the scientific evaluation by the CHMP

Budesonide Sun is a medicinal product intended to be administered into the lung and consisting of a nebuliser suspension containing the only active substance in insoluble form.

Based on submitted data, the CHMP was of the view that it was adequately demonstrated that the nebuliser suspensions of test and reference products have similar chemical and physical characteristics such as same qualitative and quantitative composition, same polymorphic form of the active substance, same CQAs that might have an impact on the dissolution and absorption of the active substance in the lung including density, viscosity, surface tension, resuspendability, sedimentation rate, pH, osmolality, particle size distribution of the suspension prior to nebulisation, with and without agglomerates and particle shape.

The CHMP was of the view that equivalence between the test and the reference product in terms of PSD has been demonstrated, since the applicant demonstrated the suitability of the Malvern Morphology G3SE-ID, the sample preparation has been clearly described and the method has been adequately validated**.**

However, some results of the comparative assessment in terms of APSD, which is the CQA that more than any other parameters allows to predict the aerodynamic performance of a product, as measured through a validated impaction method, failed to support the equivalence between the test and the reference product. The lower side of the 90% CI of the mean T/R ratio was observed outside the acceptable variability range of +/- 15% (85-117.65) for some grouped stages and is below 1 for almost all grouped stages. As the failures are only in the lower side of the CI, a systematic deviation can be identified, resulting in a lower fraction of active substance available during nebulisation for the test product.

It can be observed that the amount of active substance retained in the ampoules is larger for the test product than for the reference product, and therefore it is considered that the amount retained on the surface of the ampoules after pouring the content (from the vial to the nebuliser), may have an impact on the amount of active substance nebulised. It has been argued by the applicant that the observed differences in APSD can be attributed to the fact that the delivered dose of the test samples is lower than the delivered dose of the reference product samples. However, this cannot be confirmed since evidence to support this hypothesis has not been submitted.

The QWP has been consulted in the context of this procedure. The QWP concluded that APSD by cascade impactor is a suitable method to demonstrate comparability of the aerosolised suspension. While it was acknowledged that the method can be over-discriminatory and could potentially detect differences which are not always of clinical relevance, the QWP also highlighted, that the increased error rate should have been addressed *a priori* (e.g. increasing the power of the hypotheses) and no systematic deviations by the active substance, product strength or particle size group should be acceptable. With regards to the observed APSD differences, the impact of two potential factors (i.e. method variability and residual suspension in the vial) that could be responsible for the deviation observed, have not been fully investigated and discussed by the applicant. This position was endorsed by the CHMP.

The applicant has proposed to apply an overfill of the nebuliser suspension in the ampoule of the test product as a corrective action for the identified quality issues. However, introducing an overfill should be clearly justified during the pharmaceutical development and cannot be a mean to mitigate *a posteriori* a quality issue, thus this approach is not deemed acceptable by the CHMP in the context of this referral procedure. In addition, in the absence of supportive data generated with the product containing the overfill, it cannot be concluded that applying such overfill would indeed result in similar delivered doses poured from the ampoules and subsequently no structural trend of APSD ratio T/R < 1.

Overall, the CHMP was of the view that therapeutic equivalence between the reference and test product has not been demonstrated. In particular, it has not been proven that the aerodynamic performance of Budesonide Sun is equivalent to that of the reference medicinal product, and therefore it cannot be excluded that this would not lead to clinically relevant differences. The CHMP therefore concluded that the benefit-risk balance of Budesonide SUN is not favourable.

Overall summary of the scientific evaluation by the CHMP after re-examination

Having received a negative opinion after finalisation of the CHMP referral procedure under Article 29(4) of Directive 2001/83/EC, the applicant has requested a re-examination based on the following grounds:

First, the justification for the observed differences in the APSD assessment based on the higher net content of the reference product and the resulting justification to adjust the fill volume; second, the justifications provided for the observed differences for the APSD results are well supported by the delivered dose orientation studies; third, the acceptability of the middle and highest dosage strength based on the dose proportionality to the lowest dosage strength, for which acceptable comparative APSD behaviour to the reference product has been demonstrated; fourth, the suitability of the determination of similar PSD in the suspension for nebulisation before and after nebulisation by Morphology G31D method as surrogate of APSD assessment by impaction method.

For the first ground, the CHMP did not consider that it is adequately demonstrated that the observed APSD differences are attributed to the highest net content of the reference product and therefore the adjustment of the fill weight is not justified. In addition, the CHMP confirmed its initial position that introducing an overfill should be clearly justified during the pharmaceutical development and cannot be a mean to mitigate *a posteriori* a quality issue.

With regards to the storage orientation study, the CHMP considered that the provided data do not support the rationale that a higher net fill for the reference product accounts for the differences observed in the APSD assessment.

For the third ground of re-examination, the CHMP noted that the APSD results for the lowest strength (0.25mg/2ml) satisfactorily comply with all the requirements as laid down in the OIP equivalence guidance, however it was concluded that apart from the dose proportionality of all three dosage

strengths, a comparable APSD behavior should be demonstrated between the individual strengths of the reference and the test products.

Finally, for the fourth ground, the CHMP noted that the PSD results concerning the suspension in the ampoules can be considered similar, but did not agree that the PSD results after nebulisation obtained by Malvern Morphology G3SE-ID technology can replace the APSD assessment by impactor and therefore the PSD assessment after nebulisation by Malvern Morphology G3SE-ID technology cannot be considered as a surrogate for APSD assessment by impaction method.

In conclusion, the reasons for the observed APSD differences remain uncertain and from a quality perspective not all the requirements *as per* OIP equivalence guidance have been fulfilled. In this re-examination procedure, no new argumentation or explanation for justifying the recorded differences have been provided by the applicant. In the absence of demonstration of therapeutic equivalence based on all requirements of the OIP equivalence guidance, the CHMP confirms its initial conclusion that the benefit-risk balance of the medicinal product Budesonide SUN is not favourable.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC;
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as potential serious risk to public health, in particular the data provided in support of the demonstration of the similarity between the physiochemical properties and the quality characteristics of the reference medicinal product and those of the test medicinal product;
- The Committee noted that the results of the aerodynamic particle size distribution (APSD) comparison, which is a critical quality attribute for the particle aerodynamic performance, fell outside the pre-defined maximum allowed range of variability of +/- 15% for some grouped stages, hence the APSD results did not meet the requirements of the OIP equivalence guidance (CPMP/EWP/4151/00 Rev.1.), therefore the Committee was of the view that the equivalence of the aerodynamic performance of Budesonide Sun to that of the reference medicinal product has not been proven;
- The Committee considered the response of the Quality Working Party;
- The Committee took into consideration the grounds for re-examination submitted by the applicant and the subsequent assessment by the (Co-)Rapporteurs
- Taken together, the Committee was of the view that the available data were not sufficient to demonstrate equivalence between the reference and test product and that clinically relevant differences could not be excluded;

The Committee, as a consequence, considers that the benefit-risk balance of Budesonide SUN and associated names is not favourable.

Therefore, the Committee recommends the refusal of the marketing authorisation application of Budesonide SUN and associated names in the reference and concerned Member States.