DEMANDE D'AUTORISATION DE MISE SUR LE MARCHE

PROPIONATE DE FLUTICASONE – SALMETEROL BASE
CLL PHARMA

100 µg / 50 µg (par dose)
250 µg / 50 µg (par dose)
500 µg / 50 µg (par dose)

Poudre pour inhalation en récipient unidose

Module 5

CLINICAL STUDIES

5.1 Table of content
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.4 Litterature references

- JUIN 2012 -

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MODULE 5 :

CLINICAL STUDY REPORTS

5.1 Table of Contents of Module 5

MODULE 5 : CLINICAL STUDY REPORTS

5.2 Tabular Listing of All Clinical Studies

Not applicable.

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

The Applicant provided *in vitro* comparative data obtained with the multistaged impactor and fulfilled all of the criteria stipulated in the CPMP/EWP/4151/00 guideline to ask for clinical studies biowaiver.

The CPMP/EWP/4151/00 guideline states that "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):"

1. "The product contains the same active substance (i.e. same salt, ester, hydrate or solvate, etc.)."

Both products contain the same active substances in the same chemical structure and in the same strengths.

2. "The pharmaceutical dosage form is identical (e.g. pMDI, non-pressurised MDI, DPI, etc.)."

Both products have the same pharmaceutical dosage form in the form of powder for inhalation, are identically packed and identically delivered by the identical inhalation device type "discus".

3. "The active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product or the aerosol particle behaviour."

In both products active substance is in the same solid stage - powder for inhalation. Microscopic evaluation have shown no significant difference in crystaline structure. In vitro data confirmed equivalency in deposition characteristics and aerosol particle bahavior. As the pruducts are technically identical and sponsor presented thorough product quality data, no differences in products performance are expected even if some minor differences in crystalline/polymorhic form exist .

4. "Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g. delivered dose uniformity, etc.), aerosol particle behaviour (e.g. hygroscopic effect, plume dynamic and geometry) and/or be likely to affect the inhalation behaviour of the patient (e.g. particle size distribution affecting mouth/throat feel or "cold Freon" effect)."

Both products have the same nominal amount of the dose. Excipients used in both products are lactoses of different grades to obtain appropriate deposition. Quantity of lactose is the same in both products. As the inhalation device is the same and sponsor showed comparatibility of products performance and aerosol particle behavior any minor qualitative differences in lactoses if exists should not influence inhalation effect to the patient.

5. "Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product."

Both products have the same nominal amount of the dose. Excipients used in both products are lactoses od different grades to obtain appropriate deposition. . Asaris uses pharmacopeial grade

lactoses. Quantity of lactose is the same in both products. As the inhalation device is the same and sponsor showed comparatibility of products performance and aerosol particle behavior any minor qualitative differences in lactoses if exists should not change the safety profile of the product.

6. "The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%)."

As both products uses the same inhalation device type "discuss" and Asaris formulation was developed to mimic Seretide inhalation performance, sponsor has managed to obtain comparable amount of active substance deposition in the lungs (within +-15%) for wide range of flow rates (28,6L/min, 60 L/min and 90L/min).

7. "Handling of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar."

As both products uses the same inhalation device type "discuss", handling of the devices is identical in order to release the required amount of the active substance.

The difference in the devices is coloring and the way of marking the last 5 doses on the device counter only. Seretide device uses color difference (red color against the black). Asaris device uses dot mark.

8. "The inhalation device has the same resistance to airflow (within +/- 15%)."

Inhalation devices of both products have the same resistance to airflow (within +-15%). This sould be expected taking into account identity of inhalation devices.

9. "The target delivered dose should be similar (within +/- 15%)."

Data from the complete particle size distribution profile of a validated multistage impactor methods are provided as well as comparative *in vitro* data at different flow rates. The range of flow rates 28,6L/s, 60 L/s and 90L/s covers the whole range of intended patient population. It is the minimum (e.g. 10th percentile), median and maximum (e.g. 90th percentile) achievable flow rate in this patient population.

The *in vitro* comparison was performed using Anderson impactor with the 4 groups of stages (Levels 1 to 4) as well as Fine Particle Fraction (FPF). Sponsor has presented good justification for grouping the stages based on the expected deposition sites in the lungs. *In vitro* comparison was performed for the stages that represent the fine particle mass as well as the upper stages of the impactor which are relevant to the efficacy and safety of the medicinal product *in vivo*. Group 1 stages of impactor mimics the swallowed fraction, thus systemic exposure from the gastrointestinal tract is expected to be similar.

Criteria for in vitro equivalence were appropriately established: maximum allowable *in vitro* difference (90% of the ratio of means) should be within the range of +/- 15% in any comparison, i.e. stage, flow rate and active ingredient.

Ratio of means of deposition (Reference product/Applicant' product) are presented in the table below.

50-100 fluticasone propionate									
Level									
Level									
Level									
Level									
FPF									
FPF									
salmeterol xinafoate									
Level									
Level									
Level									
Level									
FPF									
FPF									
50-250 fluticasone propionate									
Level									
Level									
Level									
Level									
FPF									
FPF									
salmeterol xinafoate									
Level									
Level									
Level									
Level									
FPF									
FPF									
50-250 fluticasone propionate									
Level									
Level									
Level									

Level									
FPF									
FPF									
salmetrol xinafoate									
Level									
Level									
Level									
Level									
FPF									
FPI									

R- Reference product, A-Applicant' product, FPF- Fine Particle Fraction

As clinical studies biowaiver is well documented with in vitro data, this clinical overview focus on large literature data related to salmeterol, fluticasone and combination administered by inhalation.

In this overview following european guidelines are taken into account:

Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents. CPMP/EWP/239/95

Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. CPMP/EWP/4151/00

Note for guidance on the clinical investigation of medicinal products in the treatment of asthma. CPMP/EWP/2922/01

Points to consider on clinical investigation of medical products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD). CPMP/EWP/562/98.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

Not applicable.

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

Not applicable.

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

Not applicable.

5.3.5 Reports of Efficacy and Safety Studies

Not applicable.

5.3.6 Reports of Post-Marketing Experience

Not applicable.

5.3.7 Case Report Forms and Individual Patient Listings

Not applicable.