SCIENTIFIC DISCUSSION

1 INTRODUCTION

This application has been submitted to the EMEA for the CHMP to issue a scientific opinion in accordance with Article 58 of Regulation (EC) No 726/2004, in the context of cooperation with World Health Organisation (WHO) for Lamivudine/zidovudine GSK film coated tablets.

Lamivudine (2,deoxy-3'thiacytidine) and zidovudine (3'-azido-3'-deoxythymidine) are nucleoside analogue reverse transcriptase inhibitors intended for the treatment of HIV infection.

Since 1998, a medicinal product containing lamivudine/zidovudine has been authorised in the Community under the invented name Combivir as film-coated tablets (150 mg lamivudine and 300 mg zidovudine). Both substances have also been authorised as individual compounds.
Since 1987, a medicinal product containing zidovudine has been authorised under the invented name Retrovir as film-coated tablets (300 mg) capsules (100 and 250 mg), oral solution (100 mg/ml) and iv for infusion (10 mg/ml).
Since 1996, a medicinal product containing lamivudine has been authorised in the Community under the invented name Epivir as film-coated tablets (150 and 300 mg) and as an oral solution (10 mg/ml). Furthermore lamivudine has also been registered, when formulated as a constituent part of two other fixed dose combination products in which lamivudine is combined with abacavir (film coated tablets containing 300 mg lamivudine and 600 mg abacavir registered as Kivexa) or zidovudine and abacavir (film coated tablets containing 150 mg lamivudine, 300 mg zidovudine and 300 mg abacavir registered as Trizivir).

The only differences between the centrally authorised Combivir film-coated tablets and these new Lamivudine/zidovudine GSK film coated tablets are the dye colour (red) in the film coating and the embossing.

Lamivudine/zidovudine 150/300mg GSK film-coated tabletts has been submitted for the same indication as Combivir (part of antiretroviral combination therapy for the treatment of HIV infected adults and adolescents over 12 years of age) but it is intended to be used exclusively for markets outside the Community.

Quality aspects

Introduction

The applicant has submitted a complete quality module and relevant quality overall summary.
The quality data submitted for the Lamivudine/zidovudine GSK film coated tablets application is identical to the up-to-date quality data of the Combivir dossier (including all post-marketing authorisations variations filed and assessed), except for the new data related to the film-coating and the embossing.
Since the dissolution profiles of Lamivudine/zidovudine GSK film coated tablets and Combivir are similar and the formulations are almost identical (apart from the colour), bioequivalence between these two medicinal products has been accepted in this particular case.
Therefore the report provides an overview of the quality aspect and focuses only on the changes related to the film-coating and the embossing.
Further information can be found in Combivir 150mg film coated tablet European Public Assessment Report (EPAR).

Drug Substances

Lamivudine

- Manufacture

Lamivudine is manufactured by a four-stage process from the starting materials, menthyl glyoxylate hydrate and dithianediol. All reagents and intermediates have been tested satisfactorily. Pharmaceutical development has been adequately described and also it has been shown that the most thermodynamically stable form II is the one synthesised.

- Specification

Lamivudine has been fully characterised and the specification includes tests with relevant acceptance criteria for appearance, identification, assay (IR and HPLC), impurities, residual solvents, water content. Analytical methods have been fully described and validated. Reference standards have been analysed in a satisfactory manner.

Batch analysis data have been provided for 3 production batches. All batches comply with the agreed specification and indicate satisfactory uniformity.

- Stability

Three commercial batches of lamivudine have been stored up to 60 months at 30 °C / 60% RH.
Based on the stability data, a re-test period of 3 years can be applied to lamivudine when it is stored below 30 °C.

Zidovudine

Certificates of Suitability have been issued for Zidovudine by the European Directorate for the Quality of Medicines and include all the details regarding manufacture, characterization, control of drug substance, reference standards, packaging materials and stability. A re-test period of 3 years has been approved.

Drug Product

Lamivudine/zidovudine GSK film-coated tablets are red, film-coated, capsule shaped tablets engraved with "A22" on one face. Each tablet contains 150 mg of lamivudine and 300 mg of zidovudine as a single dosage unit.
The proposed tablets will be packaged in High-Density Polyethylene (HDPE) bottles with child resistant/tamper evident closures.

- Pharmaceutical Development

Pharmaceutical development is similar to that presented for the Combivir tablets since the tablet cores are identical for both products.
The only differences between the existing Combivir tablets and the new Lamivudine/zidovudine GSK film coated tablets are the composition of the film coating (Opadry red 03B25334) and the embossing (A22 on one side).

The excipients are controlled in accordance with their respective Ph Eur monograph except for the Opadry red which is tested according to in-house specification.
None of the excipients used in the production of the tablets are of animal or human origin, therefore TSE risk is excluded.

The components of the primary packaging are adequately controlled and are in compliance with European regulation on foodstuffs.

- Manufacture of the Product

The manufacturing process is identical to that for Combivir tablets in the EU. This is a conventional process consisting of sieving, blending, compression, film -coating and packaging.
The only differences for the manufacture are related to the film coating and the engraving.
Comparison of dissolution profiles between GSK film-coated tablets and Combivir film-coated tablets confirmed that the proposed tablets are similar to the existing ones.

- Product Specification

An appropriate release specification is presented for the finished product including appearance, identification (HPLC and TLC), identification of colorants, active substance(s) assay (HPLC), active substance(s) dissolution and uniformity of mass. End of shelf-life specification includes appearance, identification, impurities (HPLC), active substance(s) assay (HPLC), active substance(s) dissolution and microbial quality (not as a routine test). Analytical methods have been appropriately described and validated.

Batch analysis data have been provided for 3 full-scale production batches. All data comply with the specification and indicate consistent and reproducible manufacture.

- Stability of the Product

Stability data have been performed on 3 production-scale batches up to 9 months at 30C/60% RH (last 3 months at 30C/65% RH) and up to 6 months at 40C/75% RH.
Provided data support a shelf-life specification of 2 years when the product is stored at or below 30°C.
Based on the stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Non-clinical aspects

Lamivudine (2,deoxy-3'thiacytidine) and zidovudine (3'-azido-3'deoxythymidine) are nucleoside analogue reverse transcriptase inhibitor with potent activity against HIV-1 and HIV-2 and have been investigated in a comprehensive pharmacology, pharmacokinetics and toxicology programme.

Reports plus summary information of the preclinical studies conducted have been previously submitted and assessed by the CHMP as part of the Combivir application including variations which have been implemented after the marketing authorisation, and information can be found in the Combivir European Public Assessment Report (EPAR).

The proposed Lamivudine/zidovudine GSK film-coated tablets is identical to that currently registered with the exception of the film coating material and embossing. The new tablets will be coloured red using a proprietary film coating material, Opadry Red 03B25334. This film-coating is a widely accepted colouring material, which complies with EC directive 95/45 (for colouring matters in medicines) and is used in a number of other pharmaceutical and food products. There are, therefore, no toxicological or other safety concerns associated with its use in lamivudine/zidovudine GSK film-coated tablets.

Therefore, the CHMP considered that there are no toxicological considerations associated with the change in coloured film coat proposed for the new Lamivudine/zidovudine GSK film coated tablets that would require additional preclinical studies.

Clinical aspects

Lamivudine and zidovudine have been investigated in a comprehensive pharmacodynamics, pharmacokinetics and clinical efficacy/safety programme.

Reports plus summary information of the clinical studies conducted have been previously submitted and assessed by the CHMP as part of the Combivir application including variations which have been implemented after the marketing authorisation, and information can be found in the European Public Assessment Report (EPAR).

Combivir, in combination with other antiretroviral compounds, has been shown to reduce HIV-1 viral load and to increase CD4 cell count. Clinical end-point data indicate a significant reduction in the risk of disease progression and mortality.
In addition over the years lamivudine and zidovudine have been widely used in several large clinical trials as a component of combination antiretroviral therapy regimen with other agents of the same or different classes.

The safety of Combivir film-coated tablets, at the recommended dosing regimens, has been established since the product was launched following the first approval in the USA in November 1997 and Europe in 1998. Since first launched to November 2004, many thousands of patients world-wide are estimated to have been treated with Combivir, with an estimated 1,414,403 patient years of exposure.

The proposed Lamivudine/zidovudine GSK film-coated tablets is identical to that currently registered with the exception of the film coating material and embossing. The new tablets will be coloured red using a proprietary film coating material, Opadry Red 03B25334. As already mentioned, because this film-coating material is a widely accepted colouring material, it is not expected to impact on efficacy and safety of lamivudine/zidovudine.

Dissolution profiles demonstrated the similarity in dissolution between the Combivir film-coated tablets and the new red Lamivudine/zidovudine GSK film coated tablets. As the dissolution profiles are similar and as the formulations are almost identical (apart from the colour), bioequivalence between Combivir and the red Lamivudine/zidovudine GSK film coated tablets has been accepted in this particular case.

Lamivudine/zidovudine GSK film coated tablets is proposed to be used in the same indication with the same dose recommendations as currently authorised for Combivir film-coated tablets.

Therefore, it is concluded that there are no efficacy and safety considerations associated with the change in coloured film coat proposed for the new Lamivudine/zidovudine GSK film coated tablets that would require additional clinical data.

2. OVERALL CONCLUSIONS, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality

Based on the data provided, it has been demonstrated that the changes of the film coating and the embossing have a very little impact on the quality aspects of the product compared to Combivir and therefore the two formulations can be considered as equivalent.
Provided data support a shelf-life specification of 2 years when the product is stored at or below 30°C. However since this product could be used in climatic zones III and IV, stability studies taking into account current guidelines need to be conducted once the opinion is adopted. The applicant has given a commitment to investigate stability further (see Annex 3).

Non-clinical pharmacology and toxicology

The pharmacology and toxicology of lamivudine and zidovudine have already been established.

The new red Lamivudine/zidovudine GSK film coated tablets is proposed in the same indication, with the same dose recommendation and conditions of use as Combivir film-coated currently authorised in the EU. No non-clinical studies have been performed in connection with this application. This was

considered acceptable since the new coating will not impact on the pharmacology and toxicology properties of lamivudine.

Efficacy and safety

The efficacy of lamivudine in HIV infected patients has already been established and the safety profile has already been well defined. Combivir in combination with other antiretroviral agents is indicated for the treatment of HIV-infected adults and children over 12 years of age.

The new Lamivudine/zidovudine GSK film coated tablets is proposed in the same indication, with the same dose recommendation and conditions of use as Combivir film-coated currently authorised in the EU. No clinical studies have been performed in connection with this submission. This was considered acceptable considering the new coating tablet will not impact on the efficacy and safety of lamivudine/zidovudine.

Benefit/risk assessment

Based on the data presented, the CHMP considers that the benefit/risk ratio of Lamivudine/zidovudine GSK film-coated tablets is favourable.

Recommendation

Based on the CHMP review of the quality, safety and efficacy data, the CHMP considered by consensus that the risk-benefit balance of Lamivudine/zidovudine GSK film-coated tablets was favourable in the following indication: “indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children over 12 years of age”.