IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Clindamycin 150 mg Capsule
Clindamycin
PA0688/044/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This mutual recognition application concerns a generic version of clindamycin and is submitted under the provisions for abridged applications under Art.10 (1) of Directive 2001/83/EC as amended, and is hence a "generic" application.

With Ireland as the Reference Member State, the applicant Chanelle Medical, Ireland is applying for the Marketing Authorisation for Clindamycin 150 mg Hard Capsules in the United Kingdom. The reference product is Dalacin C 150 mg (Pharmacia) which has been authorised in the UK since 20/02/1989 (PL 00032/5007R). Essential similarity is being claimed based on the results of a bioequivalence study conducted with the test product and the UK reference product (study ref. no. CPA 116-00). The study concluded that both products were bioequivalent. This study was submitted to support the Clindamycin 150 mg Hard Capsules national application.

In 1963 a new antibiotic, lincomycin, produced by a new species of the Streptomycetaceae family, *Streptomyceslincolnesis* var. lincolnensis, was discovered. The bacteria had been isolated from an oil sample which had been extracted in Nebraska, USA. Lincomycin was licensed in 1967 in the USA for use in the treatment of infections caused by gram-positive bacteria. Numerous chemical modifications were tried to improve the pharmacokinetics of lincomycin and broaden its antibacterial spectrum. The 7-Chloro-7-deoxylincomycin derivative, clindamycin, proved to be the most effective.

Clindamycin has been marketed in Europe and in numerous non-European countries. Clindamycin hydrochloride in the form of capsules is used for oral administration. The recommended daily dose is 150-300 mg every six hours in moderately severe infection, and 300-450 mg every six hours in severe infection. The spectrum of antimicrobial activity of clindamycin includes many gram-positive and gram-negative anaerobic bacteria as well as organisms such as *Plasmodium, Toxoplasma*and *Chlamydia*. These same indications, using the same dosage, are also claimed for the proposed formulation that is the subject of this submission.

II. QUALITY ASPECTS

II.1 Introduction

Composition
The product is a hard gelatin capsule containing 150 mg Clindamycin, as Clindamycin hydrochloride, in a powder form.

All manufacturing operations are conducted in accordance with Good Manufacturing Practice. Clindamycin 150 mg is manufactured by Chanelle Medical, Loughrea, County Galway, Ireland which holds a current manufacturing licence for this product type issued by the Health Products Regulatory Authority.

II.2 Drug Substance

The active substance is clindamycin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.), which is manufactured in accordance with Good Manufacturing Practice (GMP).
The active substance specification is considered adequate to control the quality and meets the current pharmacopoieal requirements. Batch analytical data demonstrating compliance with this specification have been provided.

II.3 Medicinal Product

Composition
Clindamycin capsules contain the active substance Clindamycin hydrochloride and the following other ingredients lactose monohydrate, maize starch, magnesium stearate, purified talc, gelatine, erythrosine, indigo carmine FD&C blue, titanium dioxide. The printing ink for the capsule markings contains: titanium dioxide, IMS 74 OP, shellac, Purified water, N-butyl alcohol and soya lecithin. All excipients comply with pharmacopieal requirements or are adequately controlled by the manufacturer's specifications.
The EU guidelines on the use of gelatin derived from animal origin have been complied with.
Container / Closure System
The product is presented either as a blister pack of PVC / polyethylene / PVdC aluminium foil in an outer cardboard carton or in polypropylene containers with polyethylene tamper-evident lids.

Pharmaceutical Development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The applicant demonstrated that the product is a stable product that is essentially similar to the innovator product, Dalacin 150mg Capsules marketed in Austria and Scandinavia. This is considered equivalent to the Irish reference product.

Manufacture of the Product
The product is manufactured in accordance with conventional manufacturing techniques for this product type, dry powder blend in a hard capsule. The product is manufactured in compliance with the principles of Good Manufacturing Practice and the manufacturing process has been validated according to relevant European / ICH guidelines.

Product Specifications
The finished product specification is based on the Ph. Eur. monograph for hard capsules with some additional tests specific for this product.
Batch analytical data has been provided demonstrating compliance with the specification and thus showing the ability of the manufacture to produce finished product of consistent quality.
Product Stability
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for three years with no special precautions for storage.

Conclusion on quality
The quality of this product has been demonstrated satisfactorily.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Clindamycin has been marketed in Europe and in numerous non-European countries. Clindamycin hydrochloride in the form of capsules is used for oral administration. The recommended daily dose is 150-300 mg every six hours in moderately severe infection, and 300-450 mg every six hours in severe infection. The spectrum of antimicrobial activity of clindamycin includes many gram-positive and gram-negative anaerobic bacteria as well as organisms such as *Plasmodium, Toxoplasma* and *Chlamydia*. These same indications, using the same dosage, are also claimed for the proposed formulation that is the subject of this submission.

III.2 Pharmacology

The pharmacology of clindamycin has been well established and is extensively reviewed in the literature.

III.3 Pharmacokinetics

No new pharmacokinetic studies were presented in support of this application. The pharmacokinetics of clindamycin have been successfully established and documented within the literature and an appropriate and sufficient summary of these findings were presented.

III.4 Toxicology

No new toxicological studies were submitted in support of this application. The toxicology of clindamycin is considered to have been well established with respect to acute and chronic toxicity by the extensive duration of clinical use.

III.5 Ecotoxicity/environmental risk assessment

Clindamycin Hard Capsules is an application according to Article 10(10 2001/83/EC (as amended)- generic application.

Clindamycin is not a new drug substance and the brand leader Dalacin C has been authorised in the EU for more than 10 years.

The marketing authorisation application is for a drug product which will not be administered at a higher dose level, or for a longer duration or for different indications than were previously in effect. There is no increased environmental risk associated with the introduction of this generic. Therefore no risk assessment has been performed

III.6 Discussion on the non-clinical aspects

Clindamycin has been used in the clinical setting for an extensive period of time. The pharmacology, pharmacokinetics and toxicology (acute, chronic, reproductive etc.) have been well established. The lack of new studies presented in support of this application is considered justified and the company provided an extensive review of the literature and an appropriate assessment in support of this application. The safety and toxicological profile of the drug is considered established and no new studies were considered to be warranted.

IV. CLINICAL ASPECTS

IV.1 Introduction

This mutual recognition application concerns a generic version of clindamycin and issubmitted under the provisions for abridged applications under Art.10 (1) of Directive 2001/83/EC as amended, and is hence a "generic" application.

With Ireland as the Reference Member State, the applicant Chanelle Medical, Ireland is applying for the Marketing Authorisation for Clindamycin 150 mg Hard Capsules in the United Kingdom.

The reference product is Dalacin C 150 mg (Pharmacia) which has been authorised in the UK since 20/02/1989 (PL 00032/5007R).

Essential similarity is being claimed based on the results of a bioequivalence study conducted with the test product and the UK reference product (study ref. no. CPA 116-00).

The indications for Clindamycin 150 mg Hard Capsules are:
Clindamycin is indicated for the treatment of severe infections caused by susceptible gram-positive aerobic organisms or by susceptible anaerobic organisms.

The submitted documentation in relation to the proposed product is of sufficient high quality in view of the present European regulatory requirements. A clinical overview, which represents an adequate summary of the dossier, has been submitted.

A bioequivalence study was conducted comparing the test product to the reference product. The study concluded that both products were bioequivalent. This bioequivalence study was conducted in compliance with the Study Protocol, Declaration of Helsinki (Somerset West, 1996), current GCP and GLP guidelines, and the other applicable international and national regulatory requirements

IV.2 Pharmacokinetics

The pharmacokinetics of clindamycin have been comprehensively reviewed and the conclusions are as follows:
- Approximately 90% of an oral dose of clindamycin hydrochloride is rapidly absorbed from the gastrointestinal tract.
- Maximum plasma concentrations (C_{max}) after 600 mg clindamycin as a single oral dose vary between 5.3 and 8.0 mcg/mL with time to reach C_{max} (T_{max}) between 45 and 60 minutes.
- Absorption is not significantly diminished by food in the stomach but the rate of absorption may be reduced.
- Clindamycin is widely distributed in body fluids and tissues including bone but it does not reach the CSF. High concentrations occur in bile and it accumulates in leucocytes and macrophages.
- Clindamycin diffuses across the placenta and appears in breast milk.
- Clindamycin is approximately 93% bound to plasma proteins.
- The major active metabolites are clindamycin sulfoxide and N-demethyl clindamycin.
- Elimination half-life is 2 to 3 hours. About 10% of the dose is excreted in the urine as active drug or metabolites and about 4% in the faeces. The remainder is excreted as inactive metabolites. Excretion is slow and takes place over several days.
- Dose linearity of the pharmacokinetic characteristics is demonstrated between 150 and 600 mg.

The Summary of Product Characteristics (SPC) reflects the above information.

The product intended for marketing is a hard gelatin capsule containing 150 mg clindamycin hydrochloride. The pharmacokinetics of the 150 mg clindamycin capsule have been studied and compared with the reference product, Dalacin C capsules 150 mg (Pharmacia) (Study CPA 116-00).

The primary aim of the study was to assess the bioequivalence of CLINDAMYCIN capsules 150 mg (Chanelle Medical Ltd. Ireland) versus DALACIN C capsules 150 mg (Pharmacia and Upjohn, UK) after a single oral dose. The bioequivalence was evaluated in 26 adult healthy volunteers under fasting conditions and conducted between 11/01/2001 and 29/01/2001. The single doses of 300 mg of clindamycin as two capsules of CLINDAMYCIN capsules 150 mg(Chanelle Medical Ltd., Ireland) (Treatment T - TEST formulation) and 300 mg of clindamycin as two capsules of DALACIN C capsules 150 mg (Pharmacia and Upjohn, UK) (Treatment R REFERENCE formulation) were given with 200 ml of water to healthy subjects under fasting conditions, on two separate occasions, in the morning of Study Day 1 of each Study Period. The pharmacokinetic parameters C_{max}, t_{max}, $AUC_{o\text{-}last}$, AUC_{o_inf}, residual area, and $t_{l/2}$ were calculated from the plasma concentrations of clindamycin determined by a validated HPLC method SOP CPA MET 40-01. The bioequivalence assessment is based on the statistical evaluation of $AUC_{0\text{-}inf}$and C_{max} as primary parameters.

For $AUC_{0\text{-}inf}$, the primary variable, the point estimate was 1.13 with a 90% confidence interval (1.0224, 1.2543), For C_{max} the point estimate was 1.09 with a 90% confidence interval (0.9905, 1.1960), which also lies wholly within the bioequivalence range of 0.80 to 1.25.

The 90 % Confidence Intervals for both $AUC_{0\text{-}inf}$ and C_{max} are, therefore, within (or just on the margin in the case of $AUC_{0\text{-}inf}$) 0.8 – 1.25 and are therefore in line with the conventional acceptance criteria of 0.8 – 1.25 as defined in the Q and A document on the Bioavailability and Bioequivalence Guideline Doc Ref: EMEA/CHMP/EWP/40326/2006 which state '*For establishing bioequivalence, the 90% confidence interval should lie within the acceptance interval (in most cases, 0.80 – 1.25), the borders being included.*It was concluded that the proposed formulation of clindamycin hydrochloride was bioequivalent to the reference product, Dalacin C capsules.

The tolerance of both products was excellent. No serious adverse event or unexpected adverse drug reaction occurred during the study. No adverse event occurred. No laboratory finding in the final laboratory examination was assessed as clinically significant.

IV.3 Pharmacodynamics

The antibiotic activity of clindamycin is based on the inhibition of bacterial synthesis. Reversible coupling to the 50S subunit of the bacterial ribosome inhibits inter alia the translation or tRNA-bound amino acids, thereby preventing elongation of the peptide chain. Because of this, the mode of action of clindamycin is predominantly bacteriostatic. However, bactericidal activity can be achieved against some pathogens such as *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus* with therapeutic concentrations. This can be explained by the active accumulation of clindamycin in various human cells. Granulocytes, in whose lysosomes clindamycin has accumulated, reach sites of infection by chemotaxis. Very high clindamycin concentrations, which may be significantly higher than serum concentrations, have been measured in both sterile and infected abscesses. This explains both the bactericidal properties and antibacterial effects of clindamycin at subinhibitory concentrations. At subinhibitory concentrations, clindamycin inhibits the power of various pathogens to adhere to the surface of human cells, thereby also maintaining the immune system's power to resist infection.

IV.4 Clinical efficacy

Clindamycin is primarily a bacteriostatic antibacterial used chiefly in the treatment of serious anaerobic infections, notably due to *Bacteroides fragilis*, and in some staphylococcal and streptococcal infections. It may be used to treat liver abscess, actinomycosis, staphylococcal joint and bone infections, the carrier state of diphtheria, gas gangrene, various gynaecological infections including bacterial vaginosis, endometritis and pelvic inflammatory disease, necrotising fasciitis, secondary peritonitis, streptococcal pharyngitis, pneumonia, septicaemia and skin infections. It is used in the prophylaxis of endocarditis and in combination with other drugs for the prophylaxis of surgical infection. Clindamycin has some antiprotozoal actions and has been used in the treatment of babesiosis, malaria and toxoplasmosis in combination with other antiprotozoals. It may be used in combination with primaquine in the treatment of *Pneumocystis carinii* pneumonia. The therapeutic indications listed in the SmPC are therefore justified. Clindamycin's clinical efficacy is established for the indications sought through large numbers of clinical studies and extensive global clinical experience. The Applicant has supplied a critical review and comprehensive list of literature references that supports this marketing authorization application. The overview of clinical efficacy is adequate.

IV.5 Clinical safety

Clindamycin is reported to produce diarrhoea in up to 20% of patients after systemic administration. In some patients pseudomembranous colitis, due to toxins produced by *Clostridium difficile* may develop. This may be fatal. Other gastrointestinal effects reported with oral clindamycin include nausea, vomiting, abdominal pain or cramps. Hypersensitivity reactions, including skin rashes, urticaria and very rarely anaphylaxis, have occurred and occasionally transient leucopenia, agranulocytosis, eosinophilia, thrombocytopenia and abnormalities of liver function tests have been reported. An *in vitro* interaction with erythromycin exists and clindamycin may enhance the effect of drugs with neuromuscular blocking activity with a potential danger of respiratory depression. Clindamycin can cross the placental barrier and is excreted in human milk. The pharmacokinetics of clindamycin are unchanged in the elderly and in renal or hepatic disease.

The optimal dose ranges and dose regimens for clindamycin have been well established. Known and potential interactions are well documented and are included in the proposed prescribing information.The wording in the safety sections of the SmPC is in keeping with the published literature on the safety of clindamycin.

In conclusion, there is a large amount of accumulated experience with the use of clindamycin since it was first introduced into clinical practice. Its safety profile is well established and no new or different safety issues have been identified in the course of this review.

IV.6 Discussion on the clinical aspects

Clindamycin is widely available on the European market and its clinical pharmacology in adults and children has been well documented in published literature. The overview on the clinical pharmacology presented in support of the current application is well-referenced and is adequate. The conduct of the study with a dose of 300 mg (two capsules of 150 mg of the test and reference product) is considered acceptable given the linearity of the pharmacokinetics of clindamycin between 150 and 600 mg. The 90 % Confidence Intervals for both $AUC_{0\text{-}inf}$ and C_{max} are within (or just on the margin in the case of $AUC_{0\text{-}inf}$) 0.8 – 1.25 and are therefore in line with the conventional acceptance criteria of 0.8 – 1.25 as defined in the Q and A document on the Bioavailability and Bioequivalence Guideline Doc Ref: EMEA/CHMP/EWP/40326/2006 which state '*For establishing bioequivalence, the 90% confidence interval should lie within the acceptance interval (in most cases, 0.80 – 1.25), the borders being included*.

The study design, analytical methodology and statistical evaluation of the presented bioequivalent trial are in accordance with the recommendations of the relevant CHMP guidelines. The bioequivalence of the generic product with the referenced innovator product, marketed in the UK by Pharmacia, has been adequately demonstrated.

The therapeutic justification for the proposed formulation of clindamycin hydrochloride is based on the finding that this formulation was bioequivalent, in terms of rate and extent of absorption, to the reference product, Dalacin C capsules (Pharmacia). It is therefore expected that the efficacy and safety profiles of the proposed formulation will be similar to those of Dalacin C capsules. The SmPC adequately reflects the safety profile of this product and is in keeping with the published literature on the safety of clindamycin. Potentially the groups most likely to be at risk are those with renal or hepatic impairment, pregnant or lactating women, children and the elderly. Published data from these groups has been reviewed, and these groups are satisfactorily accounted for in the SmPC. The dosage regimen for the proposed formulation of clindamycin outlined in the SmPC is identical to that for Dalacin C capsules.

V. OVERALL CONCLUSIONS

In summary, the proposed formulation of clindamycin hydrochloride capsules, manufactured by Chanelle Medical, is essentially similar to Dalacin C capsules, based on the finding of bioequivalence of the two formulations, and is suitable for the proposed indications. The risk benefit ratio of the proposed formulation is expected to be that of Dalacin C capsules.

A readability test was carried out in order to fulfil the legal requirements of Article 59 (3) and 61 (1) of Directive 2001/83, as amended. The test was commissioned by Chanelle Medical, Loughrea, Co. Galway (The Sponsor). The test was carried out by Magmapharma Limited, Drogheda, Co. Louth (The Tester) and the report is dated 6th October 2008. The conduct of the study and the results obtained satisfy the legal requirements for User Testing.

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

In view of the existing knowledge and experience with the active substance, the available data and the known risk benefit profile it is accepted that the applicant will perform the standard pharmacovigilance activities as described in Volume 9A of 'The rules governing medicinal products in the European Union'. An additional Risk Minimisation Plan/EU-RMP is not required at present.

In view of the existing knowledge and experience with the active substance, the available data and the known risk benefit profile, a 3-yearly PSUR submission cycle is considered acceptable.

VI. REVISION DATE

July 2015