Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

DILACORT 2.5 MG GASTRO-RESISTANT TABLETS
DILACORT 5 MG GASTRO-RESISTANT TABLETS
(prednisolone)

Procedure No: UK/H/4395/001-2/DC

UK Licence No: PL 17507/0186-7

Auden McKenzie (Pharma Division) Limited

Lay summary

On 28 December 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Auden Mckenzie (Pharma Division) Limited for the medicinal products Dilacort 2.5 mg and 5 mg Gastro-Resistant Tablets (PL 17507/0186-7; UK/H/4395/001-2/DC). These medicines are only available on prescription from your doctor. Dilacort 2.5 mg and 5 mg Gastro-Resistant Tablets may be referred to as 'Dilacort' in this report.

Dilacort is used in a wide range of inflammatory and auto-immune conditions including:
- allergies, including severe allergic reactions
- inflammation affecting the:
  - lungs, including asthma
  - blood vessels and heart
  - bowel or kidneys
  - muscles and joints, including rheumatoid arthritis
  - eye or nervous system
- skin conditions
- some infections
- some cancers, including leukaemia, lymphoma and myeloma
- the prevention of organ rejection after a transplant.

Dilacort is also used to:
- boost steroid levels when the body is not making enough natural steroid on its own
- treat high calcium levels.

The active ingredient in Dilacort is prednisolone. Dilacort belongs to a group of medicines called steroids; their full name is corticosteroids. These corticosteroids occur naturally in the body, and help to maintain health and well-being. Boosting the body with extra corticosteroid (such as Dilacort) is an effective way to treat various illnesses involving inflammation in the body. Dilacort reduces this inflammation, which could otherwise go on making these conditions worse. This medicine must be taken regularly to get maximum benefit from it.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Dilacort 2.5 mg and 5 mg Gastro-Resistant Tablets outweigh the risks and Marketing Authorisations were granted.

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Module 1
Information about the initial procedure

Product Names	**UK/H/4395/001/DC:** Dilacort 2.5 mg Gastro-Resistant Tablets **UK/H/4395/002/DC:** Dilacort 5 mg Gastro-Resistant Tablets
Type of Applications	Generic, Article 10(1)
Active Substance	Prenisolone
Form	Gastro-resistant tablets
Strengths	2.5 mg and 5 mg
MA Holder	Auden Mckenzie (Pharma Division) Ltd McKenzie House Bury Street, Ruislip Middlesex, HA4 7TL UK
Reference Member State (RMS)	UK
Concerned Member State(s) (CMS)	Ireland
Procedure Numbers	UK/H/4395/001-2/DC
Timetable	Day 191 – 30 November 2012

Module 2
Summary of Product Characteristics

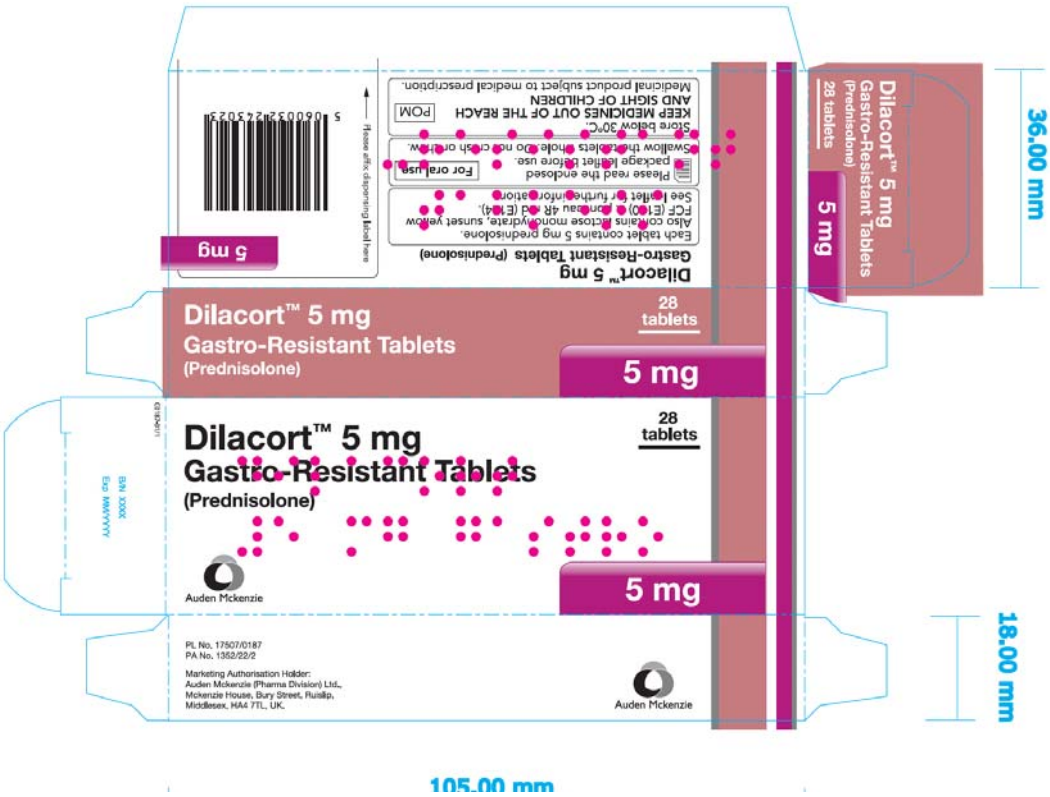
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

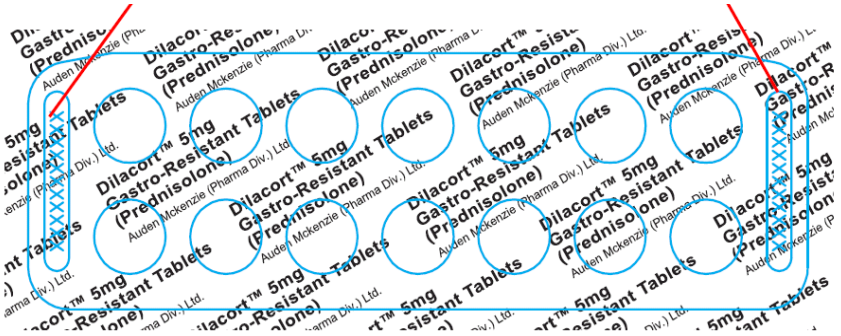
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

The labelling text below is that agreed at the end of the Decentralised Procedures. The Marketing Authorisation Holder has committed to submit the UK labelling for review to the competent authority before marketing any pack size.


Dilacort™ 5 mg
Gastro-Resistant Tablets
(Prednisolone)
28 tablets
5 mg
Auden Mckenzie
PL No. 17507/0187
PA No. 1352/22/2
Marketing Authorisation Holder:
Auden Mckenzie (Pharma Division) Ltd.,
Mckenzie House, Bury Street, Ruislip,
Middlesex, HA4 7TL, UK.
36.00 mm
18.00 mm
105.00 mm


Dilacort™ 5mg
Gastro-Resistant Tablets
(Prednisolone)
Auden Mckenzie (Pharma Div.) Ltd.

Module 5
Scientific discussion during initial procedure

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the the UK and Ireland considered that the applications for Dilacort 2.5 mg and 5 mg Gastro-Resistant Tablets (PL 17507/0186-7; UK/H/4395/001-2/DC) could be approved. The products are prescription-only medicines (POM) indicated for the following:

- **Allergy and anaphylaxis**: bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema, anaphylaxis.
- **Arteritis/collagenosis**: giant cell arteritis/polymyalgia rheumatica, mixed connective tissue disease, polyarteritis nodosa, polymyositis.
- **Blood disorders**: haemolytic anaemia (auto-immune), leukaemia (acute and chronic lymphocytic), lymphoma, multiple myeloma, idiopathic thrombo-cytopenic purpura.
- **Cardiovascular disorders**: post-myocardial infarction syndrome, rheumatic fever with severe carditis.
- **Endocrine disorders**: primary and secondary adrenal insufficiency, congenital adrenal hyperplasia.
- **Gastro-intestinal disorders**: Crohn's disease, ulcerative colitis, persistent coeliac syndrome (coeliac disease unresponsive to gluten withdrawal), auto-immune chronic active hepatitis, multisystem disease affecting liver, biliary peritonitis.
- **Hypercalcaemia**: sarcoidosis, vitamin D excess.
- **Infections (with appropriate chemotherapy)**: helminthic infestations, Herxheimer reaction, infectious mononucleosis, miliary tuberculosis, mumps orchitis (adult), tuberculous meningitis, rickettsial disease.
- **Muscular disorders**: polymyositis, dermatomyositis.
- **Neurological disorders**: infantile spasms, Shy-Drager syndrome, sub-acute demyelinating polyneuropathy.
- **Ocular disease**: scleritis, posterior uveitis, retinal vasculitis, pseudo-tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease.
- **Renal disorders**: lupus nephritis, acute interstitial nephritis, minimal change glomerulonephritis.
- **Respiratory disease**: allergic pneumonitis, asthma, occupational asthma, pulmonary aspergillosis, pulmonary fibrosis, pulmonary alveolitis, aspiration of foreign body, aspiration of stomach contents, pulmonary sarcoid, drug induced lung disease, adult respiratory distress syndrome, spasmodic croup.
- **Rheumatic disorders**: rheumatoid arthritis, polymyalgia rheumatica, juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease.
- **Skin disorders**: pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, pyoderma gangrenosum.
- **Miscellaneous**: sarcoidosis, hyperpyrexia, Behçets disease, immuno-suppression in organ transplantation.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the originator medicinal products Deltacortril 2.5mg and 5mg Gastro-resistant Tablets (PL 16853/0092-3; Alliance Pharmaceuticals Limited, UK), which were first authorised in the UK in 1976.

The active ingredient, prednisolone, is a synthetic glucocorticoid that is used clinically for its anti-inflammatory and immuno-suppressive properties. It has a predominant glucocorticoid and low mineralocorticoid activity, making it the drug of choice for the treatment of a wide range of inflammatory and auto-immune conditions.

Two bioequivalence studies were submitted to support these applications, comparing the applicant's test products Prednisolone 2.5 mg and 5 mg Gastro-Resistant Tablets (Auden Mckenzie (Pharma Division) Limited, UK) with the reference products Prednisolone 2.5 mg and 5 mg Gastro-resistant Tablets (Alliance Pharmaceuticals Limited, UK) The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 191) on 30 November 2012. After a subsequent national phase, licences were granted in the UK on 28 December 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	**UK/H/4395/001/DC:** Dilacort 2.5 mg Gastro-Resistant Tablets **UK/H/4395/002/DC:** Dilacort 5 mg Gastro-Resistant Tablets
Name(s) of the active substance (INN)	Prednisolone
Pharmacotherapeutic classification (ATC code)	Glucocorticoids, Prednisolone (ATC code: H02 AB06)
Pharmaceutical form and strength(s)	Gastro-resistant tablets; 2.5 mg and 5 mg
Reference numbers for the Decentralised Procedure	UK/H/4395/001-2/DC
Reference Member State (RMS)	United Kingdom
Concerned Member State(s) (CMS)	Ireland
Marketing Authorisation Number(s)	PL 17507/0186-7
Name and address of the authorisation holder	Auden Mckenzie (Pharma Division) Ltd McKenzie House Bury Street, Ruislip Middlesex, HA4 7TL UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

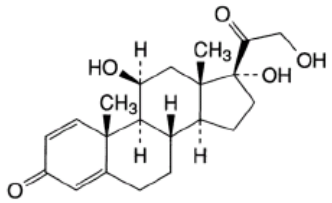
ACTIVE SUBSTANCE

INN: Prednisolone

Chemical Names:

Molecular formula: $C_{21}H_{28}O_5$

Structure:



Molecular mass: 360.4

Appearance: A white or almost white, crystalline hygroscopic powder.

Solubility: Very slightly soluble in water; soluble in methanol, and in ethanol (96 %), sparingly soluble in acetone, slightly soluble in methylene chloride.

Prednisolone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance prednisolone are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate and the coating components Opadry white, Acryl-eze white, Opadry II Brown (2.5 mg strength gastro-resistant tablet) and Opadry II Red (5 mg strength gastro-resistant tablet).

Opadry white contains hypromellose, titanium dioxide (E171), triethyl citrate and sorbic acid. Acryl-eze white contains methacrylic acid – ethyl acrylate copolymer (1:1), talc, titanium dioxide (E171), triethyl citrate, colloidal anhydrous silica, sodium bicarbonate and sodium lauril sulphate. Opadry II Brown contains polyvinyl alcohol, Macrogol 3350, talc, titanium dioxide (E171), black iron oxide (E172), red iron oxide (E172) and yellow iron oxide (E172). Opadry II Red contains polyvinyl alcohol, Macrogol 3350, Ponceau 4R red (E124) talc, titanium dioxide (E171), Indigo carmine aluminium lake (E132) and Sunset yellow FCF (E110).

Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of the coatings which are controlled to suitable in-house specifications. Black iron oxide (E172), red iron oxide (E172) and yellow iron oxide (E172) are in compliance with current EU Directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk

used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Deltacortril 2.5mg and 5mg Gastro-resistant Tablets (Alliance Pharmaceuticals Limited.) Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The gastro-resistant tablets are packaged in PVC/PVdC/Aluminium blisters packed with the Patient Information Leaflet into carboard outer cartons in a pack size of 28 gastro-resistant tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products packed in the packaging proposed for marketing. Based on the results, a shelf-life of 19 months has been proposed, with the storage conditions “Store below 30 °C.”

Bioequivalence
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section III.3, Clinical Aspects.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling text are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive

2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Forms
All aspects of the MAA forms are satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of prednisolone are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
The MAH has provided a satisfactory Environmental Risk Assessment in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP4447/00].

CONCLUSION
The grant of Marketing Authorisations is recommended.

III.3 CLINICAL ASPECTS

The clinical pharmacology of prednisolone is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Study 1
An open label randomised, two-period, two-sequence, single-dose crossover oral study comparing the pharmacokinetics of the test product Prednisolone 2.5 mg Gastro-Resistant Tablets (Auden Mckenzie [Pharma Division] Limited, UK) and the reference product Prednisolone 2.5 mg Gastro-Resistant Tablets (Alliance Pharmaceuticals Limited, UK) in healthy, adult, male, human subjects under fed conditions.

The subjects were fasted for at least 10 hours prior to a standard high fat, high calorie breakfast, which was consumed over the 30 minutes prior to dosing. The subjects were administered one tablet of either the test or the reference product with 240 ml of water, 30 minutes after the start of breakfast. Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was at least 7 days. The pharmacokinetic results are presented below:

Untransformed mean pharmacokinetic parameters (means, least square mean ratios and confidence intervals [CI]) of prednisolone.

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test (T)	Reference (R)
C_{max} (ng/mL)	96.9955 ± 22.83322	88.4742 ± 13.98503
AUC_{0-t} (ng.hr/mL)	424.7160 ± 63.50739	412.5810 ± 60.23862
$AUC_{0-\infty}$ (ng.hr/mL)	441.9386 ± 63.54062	431.5295 ± 62.21072

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity

The Geometric Least Squares Mean, Ratios and 90 % Confidence Interval for Pharmacokinetic Parameters (C_{max} and AUC_{0-t}) of prednisolone.

Pharmacokinetic Parameters (Units)	In- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test (A)	Reference (B)	T/R %	Lower	Upper
C_{max} (ng/mL)	94.6316	87.4212	108.25	100.56	116.53
AUC_{0-t} (ng.hr/mL)	420.1356	408.5514	102.84	99.47	106.31

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. Thus, the data support the claim that the applicant's test product Prednisolone 2.5 mg Gastro-Resistant Tablets is bioequivalent to the reference product Prednisolone 2.5 mg Gastro-Resistant Tablets (Alliance Pharmaceuticals Limited, UK) under fed conditions.

Study 2

An open label randomised, two-period, two-sequence, single-dose crossover oral study comparing the pharmacokinetics of the test product Prednisolone 5 mg Gastro-Resistant Tablets (Auden Mckenzie [Pharma Division] Limited, UK) and the reference product Prednisolone 5 mg Gastro-Resistant Tablets (Alliance Pharmaceuticals Limited, UK) in healthy, adult, male, human subjects under fed conditions.

The subjects were fasted for at least 10 hours prior to a standard high fat, high calorie breakfast, which was consumed over the 30 minutes prior to dosing. The subjects were administered one tablet of either the test or the reference product with 240 ml of water, 30 minutes after the start of breakfast. Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was at least 7 days. The pharmacokinetic results are presented below:

Untransformed mean pharmacokinetic parameters (means, least square mean ratios and confidence intervals [CI]) of prednisolone

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test (T)	Reference (R)
C_{max} (ng/mL)	167.5803 ± 33.12224	153.4678 ± 24.56928
AUC_{0-t} (ng.hr/mL)	796.5553 ± 195.25828	761.8462 ± 155.73079
$AUC_{0-\infty}$ (ng.hr/mL)	854.3749 ± 178.00000	824.5664 ± 154.57019

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity

The Geometric Least Squares Mean, Ratios and 90 % Confidence Interval for Pharmacokinetic Parameters (C_{max} and AUC_{0-t}) of prednisolone

Pharmacokinetic Parameters (Units)	In- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test (A)	Reference (B)	T/R %	Lower	Upper
C_{max} (ng/mL)	163.7189	151.6909	107.93	101.57	114.68
AUC_{0-t} (ng.hr/mL)	771.6967	746.7228	103.34	96.63	110.53

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. Thus, the data support the claim that the applicant's test product Prednisolone 5 mg Gastro-Resistant Tablets is bioequivalent to the reference product Prednisolone 5 mg Gastro-Resistant Tablets (Alliance Pharmaceuticals Limited, UK) under fed conditions.

Overall pharmacokinetic conclusion

The 90% confidence intervals for AUC and C_{max} were within the acceptance range for both studies. The overall conclusion is that bioequivalence between the test products and reference products under fed conditions have been adequately demonstrated.

EFFICACY

The efficacy of prednisolone is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY

With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence studies.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

The Pharmacovigilance System, as described by the Marketing Authorisation Holder, fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder 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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPCs, PIL and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION

The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The quality characteristics of Dilacort 2.5 mg and 5 mg Gastro-Resistant Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of prednisolone are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's 2.5 mg and 5 mg strength gastro-resistant tablets and and the reference products Prednisolone 2.5 mg and 5 mg Gastro-Resistant Tablets (Alliance Pharmaceuticals Limited, UK).

SAFETY

With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of prednisolone is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence studies.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with prednisolone is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome