

## **Public Assessment Report**

### **Scientific discussion**

## **Methylprednisolon Eurogenerics 4 mg and 16 mg tablets**

**(methylprednisolone)**

**NL/H/3387/001-002/DC**

**Date: 1 August 2016**

This module reflects the scientific discussion for the approval of Methylprednisolon Eurogenerics 4 mg and 16 mg tablets. The procedure was finalised on 24 February 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

## List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Methylprednisolon Eurogenerics 4 mg and 16 mg tablets, from Eurogenerics N.V.

Methylprednisolone is a glucocorticosteroid. Glucocorticoids should be considered as a purely symptomatic treatment, unless in case of certain endocrine disorders, where they are applied as substitution treatment.

Methylprednisolon Eurogenerics is indicated for:

### ***Nonendocrine disorders***

#### 1. Rheumatic disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Psoriatic arthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Ankylosing spondylitis
- Abarticular inflammations (such as acute and subacute bursitis, acute nonspecific tenosynovitis and epicondylitis)
- Acute arthritis (gouty, post-traumatic)
- Synovitis of osteoarthritis

#### 2. Collagen diseases

During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Polymyalgia rheumatica
- Giant cell arteritis

#### 3. Dermatologic disorders

- Pemphigus
- Bullous dermatitis herpetiformis
- Severe erythema multiforme (Stevens-Johnson Syndrome)
- Exfoliative dermatitis
- Mycosis fungoides
- Severe psoriasis
- Severe seborrhoeic dermatitis

#### 4. Allergic disorders

Control of severe or incapacitating allergic conditions intractable to adequate conventional therapies:

- Seasonal or chronic allergic rhinitis
- Serum sickness
- Bronchial asthma
- Drug allergy
- Contact dermatitis
- Atopic dermatitis

#### 5. Ophthalmic disorders

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

- Allergic corneal marginal ulcers
- Herpes zoster ophthalmicus
- Inflammation of the anterior segment of the eye
- Diffuse posterior uveitis and choroiditis
- Sympathetic ophthalmia

- Allergic conjunctivitis
- Keratitis
- Chorioretinitis
- Optic neuritis
- Iritis and iridocyclitis

6. Respiratory diseases

- Symptomatic pulmonary sarcoidosis
- Loeffler's Syndrome not manageable by other means
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Pulmonary disorders caused by aspiration

7. Haematologic disorders

- Idiopathic thrombocytopenic purpura in adults
- Secondary thrombocytopenia in adults
- Acquired (autoimmune) haemolytic anaemia
- Erythroblastopenia (aplastic anaemia)
- Congenital hypoplastic anaemia

8. Oncological disorders

For palliative management of:

- Leukaemia's and lymphomas in adults
- Acute leukaemia in children

9. Oedematous states

- To induce diuresis or remission of proteinuria in nephrotic syndrome, without uraemia, of the idiopathic type or that due to lupus erythematosus

10. Gastrointestinal disorders

To tide the patient over a critical period of the disease in:

- Ulcerative colitis
- Crohn's disease

11. Neurological disorders

- Acute exacerbations of multiple sclerosis
- Oedema in brain tumours

12. Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurologic or myocardial involvement
- Acute rheumatic carditis

13. Organ transplantation

**Endocrine disorders**

- Primary or secondary adrenocortical insufficiency
- (Hydrocortisone or cortisone is the drug of choice for these indications. Synthetic analogues may be used in conjunction with mineralocorticoids in certain cases; in children, mineralocorticoid supplementation is of particular importance.)
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis (De Quervain's thyroiditis)
- Hypercalcaemia as a result of cancer

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Medrol 4 mg and 16 mg tablets which have been registered in Belgium by Pfizer N.V.. The date of authorisation was 10 January 1962 for the 4 mg tablets and 12 October 1983 for Medrol 16 mg. Medrol is used as a European reference product, because the product has not been authorised in The Netherlands.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

## II. QUALITY ASPECTS

### II.1 Introduction

Methylprednisolon Eurogenerics is a tablet:

- 4 mg tablets are white to off white, round, biconvex tablets, plain on both sides.
- 16 mg tablets are white to off white, oval, biconvex tablets, with a break line on one side and embossed '16' on the other side.

The tablets are dose proportional. Each tablet contains 4 mg or 16 mg methylprednisolone. The 16 mg tablets contain a break line suitable to divide the product in equal halves.

The product is packed in packed in Al/PVC/PCTFE blisters and white HPDE bottles with polypropylene (PP) cap.

The excipients are:

- Lactose monohydrate
- Sucrose
- Sodium starch glycolate (Type A)
- Silica, colloidal anhydrous (E551)
- Magnesium stearate (E572)

### II.2 Drug Substance

The active substance is methylprednisolone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water and shows polymorphism. The results of the polymorphism study confirmed that the same polymorphic form is detected in the samples of the drug substance and drug product after manufacture and during storage, i.e. polymorphic form I.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

#### Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and additional requirements for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

#### Stability of drug substance

The active substance of both manufacturers is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

### **II.3 Medicinal Product**

#### Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. A dose proportional tablet formulation for both strengths was developed. The choice of the manufacturing process is justified. The packaging is common for this kind of dosage form. The break line on the 16 mg tablets are suitable to divide in equal halves.

Bioequivalence studies have been performed with 32 mg tablets versus Medrol 32 mg. The 32 mg batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process. Sufficient comparative dissolution data between the test and reference product have been provided.

For the 4 mg and 16 mg tablets a biowaiver was justified. The biowaiver is based on the bioequivalence study with the 32 mg product. Batches comply with the general biowaiver criteria and it has been sufficiently demonstrated that dissolution profiles of the 4 mg and 16 mg batch are similar to that of the 32 mg bioequivalence study test batch under the relevant dissolution conditions. The 4 mg, 16 mg and 32 mg tablets are fully dose proportional tablets and are manufactured using the same manufacturing process.

#### Manufacturing process

For the manufacturing of the tablets, direct compression was selected. The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

#### Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

#### Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, moisture, assay, related substances, uniformity of dosage units, dissolution and microbiological quality. All limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 2 batches of each strength have been provided, demonstrating compliance with the specification.

#### Stability of drug product

Stability data on the product have been provided for 4 batches (two for each strength) of commercial batch size stored at 25°C/60% RH (24 months), 30°C/75% RH (12-24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-PVC/PCTFE blisters and in HDPE bottles 100s count. On basis of the data submitted, a shelf life was granted of 36 months in clear PVC/PCTFE-Al blister without special storage conditions and 24 months in HDPE containers with PP cap, when stored below 30°C. Based on the results of the photostability studies the additional storage condition 'store in the original package in order to protect from light' is not necessary.

Stability data has been provided demonstrating that the product remains stable for 6 months at 25°C/60%RH in an open Petri dish. The stability profile in the open Petri dish is similar to the stability profile in the primary packaging. Therefore, stating an in-use shelf life in the SmPC is not considered necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the excipients used in this formulation are of animal origin except lactose monohydrate. A statement is provided that all raw materials used in the production of methylprednisolone tablets including lactose monohydrate have demonstrated compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

#### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Methylprednisolon Eurogenerics 4 mg and 16 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

### **III. NON-CLINICAL ASPECTS**

#### **III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Methylprednisolon Eurogenerics is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

#### **III.2 Discussion on the non-clinical aspects**

This product is a generic formulation of Medrol which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

### **IV. CLINICAL ASPECTS**

#### **IV.1 Introduction**

Methylprednisolone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

#### **IV.2 Pharmacokinetics**

##### Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Methylprednisolon Eurogenerics 32 mg tablets (Eurogenerics N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Medrol 32 mg tablets (Pfizer N.V., Belgium).

##### *The choice of the reference product*

The choice of the reference product in the bioequivalence study has been justified. The 32 mg test batch used in the bioequivalence study is of production scale and manufactured according to the finalised formulation and manufacturing process.

*Biowaiver*

A biowaiver was granted for the 4 mg and 16 mg product, based on the bioequivalence study conducted on the 32 mg strength:

- The tablets are dose proportional.
- The tablets are manufactured by the same manufacturer and manufacturing process.
- Methylprednisolone shows linear pharmacokinetics.
- The dissolution profiles of the 4 mg and 32 mg tablets are similar at pH 4.5 (more than 85% in 15 min) and pH 6.8 ( $f_2 > 50$ ). In addition similarity of the dissolution profiles at pH 1.0 was demonstrated through the Weibull method.
- The dissolution profiles of the 16 mg and 32 mg tablets are considered similar at pH 4.5 (more than 85% in 15 min), pH 6.8 and pH 1.0.

Although not registered, the choice of the 32 mg tablet used in the bioequivalence study is acceptable. It is a dose proportional formulation, representative for the 4 mg and 16 mg formulations.

*Design*

A open label, balanced, randomised, two-treatment, two-period, two-sequence, cross-over, single dose bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 19-43 years. Each subject received a single dose (32 mg) of one of the 2 methylprednisolone formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12 and 16 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. The SmPC does not indicate special dosing recommendations with regard to food intake. As such, the fasting conditions applied in the study is considered adequate.

*Analytical/statistical methods*

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*

Twenty-six healthy male subjects were included in this study. Two subjects did not report for period II for personal reasons. As such, 24 subjects complete the study and were included in the pharmacokinetic analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of 32 mg methylprednisolone under fasted conditions.**

Treatment N=24	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	2471 $\pm$ 635	2614 $\pm$ 732	368 $\pm$ 65	3.33 (1.75 – 5.0)	3.0 $\pm$ 0.7
<b>Reference</b>	2607 $\pm$ 578	2762 $\pm$ 698	430 $\pm$ 67	2.63 (1.0 – 6.0)	3.0 $\pm$ 0.6
<b>*Ratio (90% CI)</b>	0.93 (0.89 – 0.97)	--	0.85 (0.81 – 0.89)	--	--
<b>CV (%)</b>	7.9	--	10.1	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life <b>CV</b> coefficient of variation					

*\*In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC<sub>0-t</sub> and C<sub>max</sub> are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Methylprednisolon Eurogenerics 32 mg tablets is considered bioequivalent with Medrol 32 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**IV.3 Risk Management Plan**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Methylprednisolon Eurogenerics tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> <li>• Peptic ulcer</li> <li>• Growth retardation</li> <li>• Ocular effects (including central serous chorioretinopathy)</li> <li>• Hyperglycaemia</li> <li>• Adrenal dysfunction (including endocrine disorders, Cushingoid features, psychiatric disorders and behavioural changes)</li> <li>• Immunosuppression (including reactivation of quiescent viral diseases)</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Kaposi's sarcoma</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use during pregnancy</li> </ul>

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

#### **IV.4 Discussion on the clinical aspects**

For this authorisation, reference is made to the clinical studies and experience with the innovator product Medrol tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

#### **V. USER CONSULTATION**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The 16 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The test group consisted of 12 women and 8 men with an age range from 19 to 55 years. From the results of the user test, it can be concluded that patients who are prescribed this product will be able to find and understand the sought information in the PL.

#### **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Methylprednisolon Eurogenerics 4 mg and 16 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Medrol tablets. Medrol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Methylprednisolon Eurogenerics 4 mg and 16 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 February 2016.

There were no post-approval commitments made during the procedure.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY**

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached