COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Methylprednisolon ACE 100 mg tablets (methylprednisolone)

NL/H/5637/001/DC

Date: 7 July 2025

This module reflects the scientific discussion for the approval of Methylprednisolon ACE 100 mg tablets. The procedure was finalised on 19 January 2024. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MS	Multiple Sclerosis
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SAH	Subarachnoid Haemorrhage
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 ACE 100 mg tablets, from Ace Pharmaceuticals B.V.

The product is indicated for the short-term treatment of acute exacerbations of multiple sclerosis (MS).

Methylprednisolone may shorten the duration of relapses, but has no influence on relapse rate or disability progression.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. This decentralised procedure concerns a bibliographical application based on well-established medicinal use of methylprednisolone. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. Methylprednisolone 100 mg was first introduced into the European market at least ten years ago as a preoperative medication for the short-term treatment of acute exacerbations of multiple sclerosis (MS). The MAH submitted a justification for bridging between their product and the product used in the literature.

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

II. QUALITY ASPECTS

II.1 Introduction

Methylprednisolon ACE is a white to off-white, biconvex, round tablet and contains as active substance 100 mg of methylprednisolone.

The excipients are: lactose monohydrate, povidone (E1201), sodium starch glycolate, colloidal silica (E551), and magnesium stearate (E470b).

The tablets are packed in aluminium-aluminium (Al-Al) blisters in a carton box.

II.2 Drug Substance

The active substance is methylprednisolone, a white or almost white crystalline powder. It is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug

substance is practically insoluble in water and shows polymorphism. One form is consistently produced and controlled with XRPD (X-Ray Powder Diffraction) analysis.

The CEP procedure is used for 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
A CEP has 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 and meets the requirements of the monograph in the Ph.Eur. and the CEP, with an additional test for polymorphism. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (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 formulation development of the product has been briefly described, the choice of excipients is justified and their functions explained. The choice of the manufacturing process is justified. The bridging from literature to the proposed product has been adequately demonstrated. The discriminatory power of the dissolution method has been demonstrated.
The pharmaceutical development is acceptable.

Manufacturing process
The manufacturing process consists of granulation followed by direct compression. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. The functionality related characteristics have been adequately addressed. 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 description (appearance, dimensions), mass, loss on drying, resistance to crushing, disintegration time, dissolution, identification (HPLC, UV), assay, uniformity of dosage units, related substances, water activity and microbiological quality. The shelf-life specification is identical to the release specification with exception of the limit for total impurities and loss on drying. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from five commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three commercial scale batches stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (8 months) in accordance with applicable European guidelines. In addition, stability data on the product have been provided for three supportive batches (packed in less protective HDPE containers; not commercial packaging) of commercial batch size stored at 25°C/ 60% RH (21-24 months) and 40°C/ 75%RH (6-9 months). Photostability studies in line with ICH Q1B have been performed, showing that the drug product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and 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 ACE 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 Pharmacology

Primary pharmacodynamics

Methylprednisolone and its derivatives are intermediate-acting, synthetic glucocorticoids. Methylprednisolone is five times more potent in its anti-inflammatory properties compared to hydrocortisone (cortisol), but its mineralocorticoid activity is minimal (Langhoff & Ladefoged, 1983). The pharmacodynamic properties of methylprednisolone are well understood, and sufficiently described. It is widely distributed to the tissues, has high oral bioavailability, and is able to cross the blood brain barrier (Almon et al., 2002).

More specifically for the current indication, in the acute phase of MS, methylprednisolone acts in various ways to decrease the inflammatory cycle, including dampening the inflammatory cytokine cascade, inhibiting the activation of T cells, decreasing the extravasation of immune cells into the central nervous system, facilitating the apoptosis of activated immune cells, and indirectly decreasing the cytotoxic effects of nitric oxide and tumour necrosis factor alpha.

Methylprednisolone diffuses passively across the cellular membrane and binds to the intracellular glucocorticoid receptor. This complex translocates into the nucleus, where it interacts with specific DNA sequences, resulting in either enhancement or suppression of transcription of particular genes. The methylprednisolone-glucocorticoid receptor complex binds and blocks promoter sites of proinflammatory genes (Zhang, Zhang, & Duff, 1997), promotes expression of anti-inflammatory gene products (Scheinman et al., 1995), and inhibits the synthesis of inflammatory cytokines, mainly by blocking the function of transcription factors, such as nuclear factor-kappa-B (NF-kB) (Auphan et al., 1995). Like the rest of the corticosteroids, methylprednisolone also suppresses the synthesis of cyclooxygenase (COX)-2, responsible for the production of prostaglandins in damaged tissue leading to the inflammation cascade (Chen et al., 2000). By reversing capillary permeability, suppressing the migration of fibroblasts and polymorphonuclear leukocytes, controlling the rate of protein synthesis, and stabilizing lysosomes at the cellular level, methylprednisolone may control or prevent inflammation through these actions as well (Ocejo & Correa, 2021). Methylprednisolone inhibits cell-mediated immunologic functions, especially those dependent on lymphocytes. Glucocorticoid administration results in neutrophilic leukocytosis, smaller elevations in monocytes, dramatic reductions in circulating eosinophils, and lesser reductions in lymphocytes. The use of methylprednisolone and other glucocorticoids results in a reduced ability of leukocytes to adhere to vascular endothelium and exit from the circulation. Glucocorticoids impair a variety of T cell functions, and moderate-to-high doses induce T cell apoptosis while keeping B cell function and antibody production preserved (Mathian et al., 2015).

Secondary pharmacological effects

Methylprednisolone is the first drug which is used for the treatment of spinal cord injury in animals and humans (Kaptanoglu et al., 2000). An initial *in vivo* study demonstrated that pretreatment of cats with a single large intravenous dose of methylprednisolone (sodium succinate) served to protect homogenates of uninjured spinal cord from *in vitro* lipid peroxidation (Braughler & Hall, 1982; Hall, 1985). In a parallel study in which the spinal tissue levels of methylprednisolone from a single large dose were followed over time, it was observed that the time course of the antioxidant effect followed the tissue pharmacokinetics quite closely, indicative of a non-classic mechanism of steroid action (Braughler & Hall, 1982; Hall & Braughler, 1982b). The steroid had to be present in the spinal tissue in a critical

concentration in order for protection against lipid peroxidation. Subsequent to these initial studies, methylprednisolone was shown to inhibit peroxidation directly in rat brain synaptosomal membranes. Following these earlier pilot experiments, investigators found that a 30-mg/kg intravenous dose of methylprednisolone given to cats that were subjected to blunt spinal cord injury could also attenuate posttraumatic lipid peroxidation, as measured by various biochemical indices (Anderson et al., 1985). A repeated finding has been the need for much larger doses than those employed in the conventional clinical treatment of spinal injury. In addition to characterizing the ability of high doses of methylprednisolone to inhibit lipid peroxidation, extensive research has shown that high-dose methylprednisolone can also exert a number of other actions on the injured spinal cord that almost contribute to an attenuation of posttraumatic neuronal degeneration (Hall & Braughler, 1982a). Investigators believe that many of these effects are also due to the inhibition of peroxidation-related processes (Hall, 1992). Probably related to these beneficial biochemical and physiological actions, a 30-mg/kg intravenous dose has been shown to enhance the acute recovery of somatosensory evoked potentials (Young & Flamm, 1982). An additional steroid effect that may help to augment neurophysiological recovery concerns an increase in spinal neuronal excitability (Hall & Braughler, 1982b). Intriguingly, this latter action follows a dose-response curve nearly identical to the antioxidant dose-response curve, but is nevertheless a separate action since it has been defined mainly in normal uninjured animals.

While a much less complete analysis is available, there is experimental evidence that the neuroprotective properties of methylprednisolone, extensively studied in spinal cord injury, are also applicable to brain injury. The steroid has been shown to enhance the early recovery of mice subjected to a moderately severe concussive head injury when administered at 5 minutes post injury. The dose-response curve for this effect is remarkably similar to that discussed above for spinal cord injury (Hall, 1985). A 30-mg/kg intravenous dose was observed to be optimum while lower (15-mg/kg) and higher (60- and 120-mg/kg) doses were ineffective. In the same study, two other glucocorticoids were compared with methylprednisolone. Prednisolone sodium succinate, given in steroid-equivalent doses with methylprednisolone, was equally efficacious but half as potent in that a 60-mg/kg intravenous dose was found to be optimum. Hydrocortisone was ineffective in improving neurological recovery in injured mice at any dose. This structure activity relationship parallels the relative abilities and potencies of these three steroids as inhibitors of lipid peroxidation (Braughler, 1985). Methylprednisolone and prednisolone are equally efficacious as lipid antioxidants *in vitro*, but the latter is half as potent. Hydrocortisone is ineffective as an inhibitor of lipid peroxidation, even at exceedingly high concentrations. Dexamethasone, a steroid widely used in neurosurgery, also possesses lipid antioxidant activity, but is slightly less effective than methylprednisolone or prednisolone.

Dating back to the 1960's, there has been a history of experimental and clinical attempts to apply glucocorticoid steroids to the acute treatment of cerebral ischemia or ischemic stroke. There is only a small amount of experimental literature considering methylprednisolone specifically. In one study using a gerbil model of 3-hour unilateral carotid occlusion followed by reperfusion, methylprednisolone significantly improved early post-reperfusion neurological recovery (Braughler & Lainer, 1986). Lower and higher intraperitoneal doses were less effective. In another study with a gerbil global ischemia model involving 60 minutes of bilateral carotid occlusion, a 30-mg/kg intraperitoneal dose given 30 minutes before

induction of ischemia was shown to cause better preservation *ex vivo* of Na+, K+-ATPase activity (Palmer et al., 1985) and cyclic adenosine monophosphate (Taylor, Palmer, & Callahan, 1984).

Safety pharmacology studies

The MAH has provided an adequate review of adverse events associated with methylprednisolone. The most common adverse events are those shared with other corticosteroids and are infections (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs), Cushing's syndrome, adrenal insufficiency, sodium retention, fluid retention, affective disorder (including depressed and euphoric mood), cataracts, hypertension, peptic ulcer, skin atrophy, acne, muscular weakness, growth retardation, impaired healing, and decreased blood potassium. The safety profile is in general reflected in the SmPC sections (4.3 to 4.9).

Experience with methylprednisolone acetate in (placebo-controlled) studies in children and adolescents is limited. Therefore, it is not possible to make a general statement about the safety profile of methylprednisolone acetate when used in children and adolescents. Corticosteroids cause growth retardation in infancy, childhood and adolescence. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Infections, which have a more serious or even fatal course with concomitant use of gluco-corticosteroids (e.g. chickenpox or measles), are more common in children than in adults (see SmPC section 4.4). Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure. High doses of corticosteroids may produce pancreatitis in children.

III.2 Pharmacokinetics

Methylprednisolone is a well-known substance and the pharmacokinetic properties are well understood. The submitted data are considered sufficient.

Glucocorticoids are well absorbed after oral administration and have a bioavailability of 60–100% (Derendorf et al., 1985) (Varis, Kivistö, Backman, & Neuvonen, 2000) (Duggan et al., 1975), although the exact bioavailability of methylprednisolone in humans is unknown. Corticosteroids are metabolized through enzymatic transformations that diminish their physiologic activity and increase water solubility to enhance their urinary excretion. Glucocorticoid metabolism is a two-step process which occurs primarily in the liver (Maser, Völker, & Friebertshäuser, 2002) (Diederich et al., 2002). The kidney excretes the resulting hydrophilic inactive metabolites (Czock et al., 2005). The terminal half-life of methylprednisolone was approximately 0.5 h after intravenous administration and approximately 1.1 h after intramuscular administration (Hazra et al., 2007).

III.3 Toxicology

Most of the toxic effects of methylprednisolone are caused by exaggerated pharmacology. Since the current product is intended to be administered only for short periods (three consecutive days), effects related to continued exposure to exogenous adrenocortical steroids are not expected. Data regarding acute overdoses of glucocorticoids are rare. The oral LD_{50} of

methylprednisolone in rats is >4g/kg, the intraperitoneal LD_{50} in mice is 2292mg/kg and in rats is 100mg/kg (Pubchem, 2021).

Methylprednisolone has not been formally evaluated for genotoxicity. The corticosteroids hydrocortisone and dexamethasone have shown genotoxic and cytotoxic activity in different *in vitro* and *in vivo* studies (Bali et al., 1990; Singh et al., 1994). However, studies using structurally related analogues of methylprednisolone (methylprednisolone sulfonate (Aaron, et al., 1989b; Aaron, Stankowski, & Zimmer, 1989), methylprednisolone suleptonate (Aaron et al., 1989a) and prednisolone farnesylate (Otsuka et al., 1992) showed no evidence of a potential for genetic and chromosome mutations in limited studies in bacteria and mammalian cells.

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. However, several related glucocorticoids can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats (Ryrfeldt, Squire, & Ekman, 1992).

Methylprednisolone has not been evaluated in animal fertility studies. Corticosterone, however, has an (reversible) adverse effect on male fertility (Lerman et al., 1997). Methylprednisolone administered during pregnancy did increase the frequency of cleft palate in mice. In addition, a decreased incidence of viable foetuses and significant increases in the incidence of dead foetuses, dead embryos and resorptions was observed (Zawoiski, 1980). Pups of rats treated with methylprednisolone showed an increase in cardiovascular effects as well as decreased body weight. High frequencies of fatal death and a variety of central nervous system and skeletal anomalies were reported in the offspring of pregnant rabbits treated with methylprednisolone in doses less than those used in humans (Zawoiski, 1980). Since safety margins for the reported teratogenic effects are unknown, the relevance to humans is not clear. The SmPC includes the relevant information.

No references on the effect of methylprednisolone on local tolerance are available. Considering the oral route of administration, the used formulation and use of the compound for decades in humans, nonclinical local tolerance data are not considered necessary.

Limits for impurities have been set and are acceptable. There is no toxicological concern regarding the present impurities.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		Log K_{ow} = 2.10	Potential PBT: No
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.00925	µg/L	> 0.01 threshold: No

Conclusion on studies

Methylprednisolone is not a persistent, bioaccumulative, and toxic (PBT) nor a very persistent, very bioaccumulative and toxic (vPvB) substance. Considering the above data, methylprednisolone is not expected to pose a risk to the environment.

III.5 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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.

IV.2 Pharmacokinetics

Since this application concerns an application based on Article 10a of Directive 2001/83, as amended, referring to (non-)clinical studies described in published literature, the MAH submitted bridging data to demonstrate that the product applied for is similar to the product(s) described in literature.

Most information in published literature of (non-)clinical studies on methylprednisolone and its use for treatment of acute exacerbations of multiple sclerosis is derived from intravenous (IV) formulations. The MAH did not attempt to demonstrate that bioavailability of the tablets applied for, and intravenous (IV) formulations is comparable. However, the MAH refers to literature in support of comparable efficacy between oral and IV methylprednisolone for treatment of an exacerbation. Most important literature for the comparison of oral and IV methylprednisolone are the studies by Ramo-Tello et al. (2014) and Le Page et al. (2015). Since the study by Le Page et al. has a more robust study design, more subjects are included, and the same posology is used as proposed by the MAH, this study is regarded as most important for the conclusion of similar efficacy for both oral and intravenous methylprednisolone.

Comparable efficacy between oral and IV methylprednisolone for treatment of an exacerbation is sufficiently demonstrated and therefore the MAH focusses on the comparison

between the product applied for, and the oral products used in the literature. The MAH thus provides a comparison of Methylprednisolone ACE tablets with compounded capsules produced by the MAH, in the form of comparative dissolution data.

These dissolution experiments demonstrate faster dissolution for the tablets compared to the compounded capsules. The relationship between *in vitro* dissolution and bioavailability of methylprednisolone is unknown. However, if there is any relation between these two, it can reasonably well be expected that faster dissolution would lead to faster absorption of methylprednisolone. If this faster dissolution will lead to a difference in bioavailability, it will likely be an exposure profile resembling exposure following IV administration of methylprednisolone, for which sufficient literature was provided. Thus, since safety and efficacy has been established for IV methylprednisolone, this possible faster absorption of methylprednisolone is not expected to be clinically relevant.

Composition of the compounded capsules used in the Le Page study was also provided. These capsules are comparable to the capsules produced by the MAH in the dissolution experiment by means of excipients with known effects to dissolution or absorption. Therefore, the compounded capsules produced by the MAH are sufficiently representative for the compounded capsule used in the Le Page study.

Consequently, the dissolution tests provided by the MAH comparing the Methylprednisolone ACE tablets with compounded capsules produced by the MAH are supportive of a bridge between the ACE tablets and the product(s) described in scientific literature.

IV.3 Pharmacodynamics

The MAH has provided a general overview of the mechanisms of action of methylprednisolone. This synthetic glucocorticoid regulates gene expression subsequent to binding specific intracellular receptors and translocation into the nucleus (Meduri & Chrousos, 2020). Methylprednisolone exerts a wide array of physiologic effects including anti-inflammatory, immunosuppressive and anti-allergic effects. For the treatment of relapses in MS specifically, the MAH indicates that the main mode of action is decrease of the inflammatory cycle.

The MAH has discussed some important secondary pharmacodynamics of methylprednisolone, relevant for the adverse events profile of dominantly chronic corticosteroids use. The warnings and precautions included in the SmPC are considered supported by data.

Data indicates that the combination of cyclosporin and high-dose methylprednisolone may increase the risk for convulsions (Durrant, Chipping, Palmer, & Gordon-Smith, 1982) This is appropriately reflected in the SmPC.

IV.4 Clinical efficacy

The MAH submitted a justification for bridging between their product and the product used in the literature. This included some comparison to placebo but also comparison to IV route

of administration. The most relevant is the Cochrane review by Filippini et al. (2000) which includes 4 randomized double blind placebo controlled published trails on methylprednisolone (MP) (Durelli et al., 1986; Milligan 1987; Filipović et al., 1997; Sellebjerg 1998) in 140 participants. The review concluded that: administration of methylprednisolone or adrenocorticotropic hormone (ACTH) favoured recovery from acute exacerbation in MS participants. Use of either agent decreased the probability of the condition getting worse or stable within the first five weeks of treatment by more than 60%. Based on these results and in combination with the additional data discussed by the MAH, the efficacy of MP for acute exacerbation in MS can be considered substantiated. The differences between oral and IV steroids in promoting disability recovery in MS relapses, was further investigated in the Cochrane review by Burton et al. (2012), Ramo-Tello et al. (2014) and Le Page et al. (2015). Generally, the differences were only numerical and not statistically significant as clearly shown in the review by Filippini et al. (2000). The numerical differences from the Cochrane review could be due to a lower dosing regimen as now also proposed by the MAH. Le Page et al. (2015) has the same dosing regimen as proposed by the MAH and here the differences were minimal; the proportion responders was 81% for oral treatment and 80% for IV treatment (treatment difference of 0.5% (90%CI -9.5%;10.4%). Change in EDSS (Expanded Disability Status Scale) score from baseline also did not differ (-0.13 (95%CI -0.42; 0.16).

IV.5 Clinical safety

Short-term corticosteroid use is associated with generally mild side effects, including cutaneous effects (Stratakis et al., 1998), electrolyte abnormalities (Williams et al., 1988), hypertension (Newton & Cooper, 1994), hyperglycemia (Arner et al., 1983), pancreatitis (Barr & Wolff, 1957), hematologic (Kelly et al., 1998), immunologic (Dale et al., 1974; Vollmer, 2007; MacGregor et al., 1969), and neuropsychologic effects (Warrington & Bostwick, 2006), although occasionally, clinically significant side effects may occur. Long-term corticosteroid use may be associated with more serious sequel, including osteoporosis (Dykman et al., 1985), aseptic joint necrosis, adrenal insufficiency (Graber et al., 1965), gastrointestinal (Liu et al., 2013), hepatic, and ophthalmologic effects (Oray et al., 2016), hyperlipidemia (El-Shaboury & Hayes, 1973), growth suppression (Allen, Julius, Breen, & Attie, 1998), and possible congenital malformations.

The most frequently reported adverse events during clinical studies conducted with MS patients were gastric pyrosis, anxiety, and insomnia. Dysgeusia, particularly metallic taste, was reported by patients who were treated with oral methylprednisolone. This was the only adverse event more frequent among patients who received oral methylprednisolone instead of intravenous methylprednisolone. Other adverse events were cutaneous rash and hypertrichosis. Most of these adverse events decreased after one week (Martinelli et al., 2009).

The tolerability of methylprednisolone was similar for both oral and intravenous regimes, except for insomnia, which was more frequent in patients receiving oral methylprednisolone than in patients receiving methylprednisolone intravenous. Insomnia might be caused due to prolonged bioavailability when methylprednisolone is administrated orally. To prevent insomnia, it is recommend in the SmPC to give the oral treatment in the morning. None of the described clinical studies reported a serious adverse effect.

Clinical experience suggests no abnormalities of children of mothers treated with usual doses of prednisone and methylprednisolone throughout pregnancy, but premature rupture of amniotic membranes and low birthweight babies may occur (Reinisch et al., 1978; Scott, 1977). Clinical findings showed that very low levels of methylprednisolone were transferred into breast milk. The necessary information is available in the SmPC.

The literature and the cases describe the effects of methylprednisolone in low dose and long-term use. No data about overdose, dependence, rebound or drug abuse is available on high-dose and short-term use of methylprednisolone. It can be concluded that oral methylprednisolone at an equivalent high dose is as safe as intravenous treatment.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version v0.2, signed 29 November 2023), 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 ACE.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to literature No new clinical studies were conducted. Risk management is adequately addressed. Altogether it is considered that the efficacy of methylprednisolone for the short-term treatment of acute exacerbations of multiple sclerosis (MS). The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. For design and lay-out the MAH refers to the tested leaflet of Acecort (NL/H/5319/001-004/MR). For content the MAH refers to Methylprednisolon Eurogenerics (NL/H/3387/002). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Methylprednisolon ACE 100 mg tablets have a proven chemical-pharmaceutical quality. Methylprednisolon is a well-known medicinal product with an established favourable efficacy and safety profile.

In the Board 1044th meeting of 4 January 2024, the following major objection was discussed: incomplete description of the qualitative and quantitative composition of the tablets in the literature is provided. This means that the assessment of whether the capsules in the literature are representative for the medicinal product cannot be made. Furthermore, the descriptions are important in order to determine whether the dissolution profiles allow for bridging of the data presented in the literature. The MAH provided the required description before the end of the application process, resolving the major objection.

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 sufficient bridging has been demonstrated for Methylprednisolon ACE with the literature reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 January 2024.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5637/ 001/IA/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority	Yes	19-2-2025	Approved	-