15 October 2020
EMA/78138/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Dexamethasone Taw

International non-proprietary name: dexamethasone phosphate

Procedure No. EMEA/H/C/005740/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
CNS	Central Nervous System
CDMS	Clinically Definite Multiple Sclerosis
COX	Cyclooxygenase
CRP	C-Reactive Protein
CYP3A4	Cytochrome P450 3A4
Disease duration	Time from disease onset, i.e. time from first clinical event
DNA	Deoxyribonucleic Acid
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GTR	Glatiramer acetate 20 mg/ml, solution for injection in prefilled syringe produced by Synthon BV
HIV	Human Immunodeficiency Virus
HPA axis	Hypothalamic, Pituitary, Adrenal axis
IFN-β	Interferon-β
IL-6	Interleukin 6
IPIR	Immediate Post-Injection Reaction
LDH	Lactic Acid Dehydrogenase
LISR	Local Injection Site Reaction
MAA	Marketing Authorization Applications
MASCC	Multinational Association for Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome-Related Corona Virus
MFSC	Multiple Sclerosis Functional Composite
MRI	Magnetic Resonance Imaging

NCCN	National Comprehensive Cancer Network
NHS	National Health Service
RNA	Ribonucleic acid
PLA2A	Phospholipase A2
PO	Per Os, orally
PT	Preferred Term
(RR)MS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SARS-CoV	Severe Acute Respiratory Syndrome-Related Corona Virus
SC	Subcutaneous
SPC	Summary of Product Characteristics
UK	United Kingdom
US(A)	United States (of America)
UV-VIS	Ultraviolet–Visible
US NLM	United States National Library of Medicine

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Dexamethasone Taw 4 mg/ml solution for injection/infusion and Dexamethasone Taw 10 mg/ml solution for injection/infusion in the treatment of:

Systemic administration:

- cerebral oedema associated with cerebral tumour, neurosurgical procedures, cerebral abscess, bacterial meningitis (e.g. tuberculosis, typhoid, brucellosis)
- polytraumatic shock/prophylaxis of post-traumatic shock-lung syndrome
- severe, acute asthma attack
- initial parenteral treatment of extensive, acute, severe skin diseases like erythroderma, pemphigus vulgaris, acute eczema
- initial parenteral treatment of autoimmune diseases like systemic lupus erythematosus (especially visceral forms)
- active rheumatoid arthritis with a severe, progressive course, e.g. fast proceeding destructive forms and/or with extra-articular manifestations
- prophylaxis and treatment of post-operative or cytostatic-induced vomiting as part of anti- emetic regimens.
- treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation)

Local administration:

- intraarticular injection: persistent inflammation of one or a few joints after general management of chronic inflammatory joint diseases, activated osteoarthritis, acute forms of periarthropathia humeroscapularis
- infiltration therapy (when strictly indicated): non-bacterial tendovaginitis and bursitis, periarthropathy, insertional tendinopathy
- ophthalmology: subconjunctival administration in non-infectious keratoconjunctivitis, scleritis (except necrotising scleritis), uveitis anterior and intermedia.

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Major objections were identified in relation to quality, quality/safety and efficacy.

The quality major objection is in relation to request for a valid GMP certificate for the manufacturing site Mylan Laboratories Limited.

The multidisciplinary major objection in quality and clinical safety is in relation to the presence of the excipients methylparaben and propylparaben in Dexamethasone Taw.

The efficacy major objections are outlined below.

- In relation to the COVID-19 indication, the proposed wording of the indication is not agreed.

- In relation to the non-COVID-19 indications, some differences as compared to the innovator product were noted and for these differences no adequate literature data support were provided.

Questions to be posed to additional experts

Not applicable.

Inspection issues

GMP inspection(s)

A request for GMP inspection is required for the following site in order to verify the GMP compliance status. The outcome of this/these inspection is required for the Committee to complete its examination of the application and will be needed.

Manufacturing, primary & secondary packaging, testing and release	Mylan Laboratories Limited (Specialty Formulation Facility), Plot No.284 B/1, Bommasandra Jigani Link Road Industrial Area, Anekal Taluk, Bangalore - 560 105, India

GCP inspection(s)

Not applicable.

New active substance status

Not applicable.

Additional data exclusivity /Marketing protection

Not applicable.

Similarity with authorised orphan medicinal products

It is considered that Dexamethasone Taw 4 mg/ml and 10 mg/ml solution for injection/infusion is not similar to Granupas, Deltyba, Pretomanid FGK, Sirturo and Verkazia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Derogation(s) from market exclusivity

Not applicable.

1. Executive summary

Justification	Assessment
Specific derogations foreseen in the legislation, with particular reference to Annex I of Directive 2001/83/EC, as amended	Mention specific derogations and confirm the reasons why the application fulfils the conditions for applying them.
Specific derogations foreseen in guidelines, with particular reference to ICH/CHMP or EC guidelines	Mention guidelines and specific derogations, and give reasons why the application fulfils the conditions for applying them.
Due to the extent of scientific knowledge the conduct of certain clinical trials is considered unethical[1-2], or the conduct of certain animal tests is considered to lead to unnecessary use of animals[3] (for instance, due to extensive clinical experience certain toxicological tests are considered unnecessary)	Discuss what evidence is the basis for the scientific knowledge, the relevance and reliability of such evidence, and assess the validity of any extrapolation. Given that evidence, assess whether repeating certain trials/tests (or conducting additional tests) would extend scientific knowledge essential for biosimilarity assessment (in case of biosimilars) or benefit/risk assessment and provision of adequate information to patients and prescribers

[1] Requirements of GCP principles of Directive 2001/20/EC, Directive 2005/28/EC and Directive 2001/83/EC as amended by Directive 2003/63/EC

[2] Requirements of GCP principles of Directive 2001/20/EC, Directive 2005/28/EC and Directive 2001/83/EC as amended by Directive 2003/63/EC (Declaration of Helsinki provides a useful reference also)

[3] Council Directive on Animal Welfare 86/609/EEC and Council Decision on the European Convention of the Protection of Vertebrae Animals.

1.1. Problem statement

1.1.1. Disease or condition

In December 2019, pneumonia was caused by a new coronavirus spread in Wuhan, China. Unbiased sequencing of samples from patients with pneumonia revealed a previously unknown type of beta-coronavirus which is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). The causative agent was named severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) by the Coronavirus Study Group and the disease it caused was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).

Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects including cerebral oedema associated with cerebral tumour, severe skin diseases, autoimmune diseases and rheumatoid arthritis.

Dexamethasone is also being used as prophylaxis and treatment of post-operative or cytostatic-induced vomiting as part of anti- emetic regimens.

Dexamethasone is also given as intraarticular injection or as infiltration therapy for various orthopedic indications.

Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU.

1.1.2. Epidemiology

On 11 March, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a pandemic.

Globally, to date approximately 30 million confirmed cases of COVID-19 have been reported.

Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, cases have been reported in all continents.

1.1.3. Aetiology and pathogenesis

COVID-19 is the disease caused by the SARS-CoV-2 virus. Coronaviruses are enveloped positive-stranded RNA viruses. Full-genome sequencing and phylogenic analysis indicated that the coronavirus that causes COVID-19 is a betacoronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus, but in a different clade.

Early in infection, SARS-CoV-2 targets cells, such as nasal and bronchial epithelial cells and pneumocytes, through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. The type 2 transmembrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which mediates coronavirus entry into host cells. ACE2 and TMPRSS2 are expressed in host target cells, particularly alveolar epithelial type II cells. Profound lymphopenia may occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, the viral inflammatory response, consisting of both the innate and the adaptive immune response impairs lymphopoiesis and increases lymphocyte apoptosis.

In later stages of infection, when viral replication accelerates, epithelial-endothelial barrier integrity is compromised. In addition to epithelial cells, SARS-CoV-2 infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils. Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early-phase acute respiratory distress syndrome (ARDS). In severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur.

The development of viral sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, may further contribute to multiorgan failure.

1.1.4. Clinical presentation, diagnosis and stage/prognosis

Presentations of COVID-19 have ranged from asymptomatic/mild symptoms to severe illness and mortality. Common symptoms have included fever, cough, and shortness of breath. Other symptoms, such as malaise and respiratory distress, have also been described. Symptoms may develop from 2 days to 2 weeks following exposure to the virus.

1.1.5. Management

Remdesivir is a 'viral RNA polymerase inhibitor' (a medicine that interferes with the production of viral genetic material, preventing the virus from multiplying) given by infusion (drip) into a vein. Remdesivir

has been authorised in the European Union under the invented name Veklury, since 3 July 2020. There are no other therapies approved in the EU for the treatment of Covid-19 infections. However, a number of therapies are under investigation.

Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU.

1.2. About the product

Dexamethasone is a mono-fluorinated glucocorticoid with pronounced anti-allergic, anti-inflammatory and membrane-stabilising properties and effects on carbohydrate, protein and fat metabolism. Dexamethasone has an approximately 7.5 times greater glucocorticoid effect than prednisolone and prednisone and compared to hydrocortisone, it is 30 times more effective, lacking mineralocorticoid effects.

The proposed product, dexamethasone sodium phosphate 4 mg/mL and 10 mg/mL solution for injection/infusion, is an aqueous IV solution containing the same the same active substance in the same concentration and similar excipients as the reference product (Fortecortin).

1.3. The development programme/compliance with CHMP guidance/scientific advice

No scientific advice was obtained from the CHMP.

1.4. General comments on compliance with GMP, GLP, GCP

GCP

Not applicable

No clinical studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases.

GMP

The manufacturing site for the medicinal product, Mylan Laboratories Limited (Plot No.284 B/1, Bommasandra Jigani Link Road Industrial Area, Anekal Taluk, Bangalore - 560 105) India was inspected by UK authorities in 2013. The manufacturing site should be inspected. See also quality assessment report and inspection issues in section 1 of this document.

GLP

No new non-clinical studies have been conducted. Reference is made to literature, with unknown GLP status. This is considered acceptable, in view of the well-known non-clinical and clinical safety profile.

1.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83, as amended, a hybrid application.

No clinical studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases.

PRIME

Not applicable

Accelerated assessment

The applicant requested accelerated assessment of this application on the basis of the unmet medical need of treatments for COVID-19.

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the assessment of the request provided by the applicant, the CHMP guideline on the procedure for accelerated assessment in the context of COVID-19 pandemic and it was recommended to grant the accelerated assessment procedure for Dexamethasone Taw.

Conditional marketing authorisation

The applicant has not applied for a conditional marketing authorisation.

Marketing authorisation under exceptional circumstances

The applicant has not applied for a marketing authorisation under exceptional circumstances.

Biosimilarity

Not applicable.

Additional data exclusivity/ marketing protection

Not applicable.

New active substance status

Not applicable.

Orphan designation

Not applicable.

Similarity with orphan medicinal products

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Information on paediatric requirements

Not applicable.

2. Scientific overview and discussion

2.1. Quality aspects

The finished product is presented as solution for injection/infusion containing 4/mg/ml and 10 mg/ml of dexamethasone phosphate (as dexamethasone sodium phosphate) as active substance.

Other ingredients are: methyl parahydroxybenzoate, propyl parahydroxybenzoate, disodium edetate, sodium citrate, anhydrous, sodium hydroxide, citric acid, anhydrous and water for injection

The product is available in amber glass vial (type 1) closed with a (bromobutyl) rubber stopper and aluminium seal with flip-off cap, containing 1 ml, 5 ml or 30 ml of Dexamethasone Taw 4 mg/ml solution for injection/infusion or 10 ml of Dexamethasone Taw 10 mg/ml solution for injection/infusion.

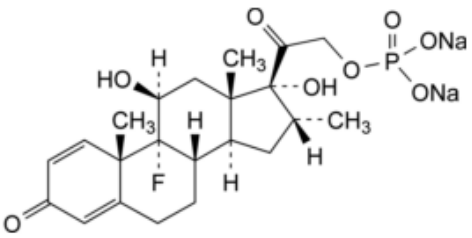
2.1.1. Active Substance

General Information

International non-proprietary name (INN): Dexamethasone sodium phosphate

Molecular formula: $C_{22}H_{28}FNa_2O_8P$

Relative molecular mass: 516.4



Dexamethasone sodium phosphate is a white to almost white crystalline very hygroscopic powder. It contains eight asymmetric carbon atoms. It is freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. A 1% solution in water has a pH between 7.5 and 10.5. Dexamethasone shows polymorphism. It should be stored in airtight containers protected from light.

There is a monograph for active substance dexamethasone sodium phosphate in the European Pharmacopoeia. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for dexamethasone sodium phosphate which has been provided within the current Marketing Authorisation Application.

Manufacture, process controls and characterisation

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The applicant's drug substance specification is in line with the Ph. Eur. monograph for dexamethasone sodium phosphate,. It includes: appearance (visual), identification (Ph.Eur.), appearance of solution (Ph.Eur.), pH (Ph.Eur.), specific optical rotation (Ph.Eur.), related substances (Ph.Eur.), inorganic phosphate (Ph.Eur.), bacterial endotoxins (Ph.Eur.), water (Ph.Eur.), assay (Ph.Eur.) and microbial limits (Ph.Eur.)

Additional specifications have also been set for residual solvents (GC). All additional methods have been adequately validated and described according to ICH Q2.

A drug substance specification has been provided by the Applicant. Clear reference was made to current Ph. Eur. Monograph for Dexamethasone Sodium Phosphate. Analytical methods are referenced either to PhEur monograph or to CEP annexes. The related substances are sufficiently controlled by the monograph and no additional impurities are described above the reporting threshold. The analytical methods are in line with the Ph. Eur. monograph and the CEP (residual solvents). Identity testing should be limited to 'First identification ' (**OC**). The testing of bacterial endotoxin and microbial limits in Dexamethasone Sodium Phosphate is performed based on Ph. Eur. 2.6.14 and Ph. Eur. 2.6.12, respectively. The drug product manufacturer has validated the test method for bacterial endotoxin and microbial limits.

Batch analysis data for dexamethasone sodium phosphate from the drug substance manufacturer; and drug product manufacturer (Mylan) are provided. All results are well within the specification. Validation of analytical methods has been reported for endotoxin and microbial limits. Other methods are considered to be fully covered either by European Pharmacopeia, or CEP Annex 2.

The Applicant has been notified about the use of EPCRS standards instead of USPRS, where possible. (**OC**)

No separate data on container closure system and stability has been provided, as it is covered by CEP.

The CEP describes the container closure system

Stability

The CEP includes a re-test period of 60 months if stored at the defined storage conditions in the commercial pack.

Finished Medicinal Product

Description of the product and Pharmaceutical Development

Dexamethasone Taw 4 mg/ml and 10 mg/ml solution for injection/infusion is a clear, colourless solution free from visible particles filled in amber glass vials with rubber closures and aluminium seal.

The container closure system consists of type I tubular amber glass vials with dark grey bromobutyl rubber stopper coloured flip-off aluminium seals. 4 mg/ml is presented in 2 ml vials (1 ml fill), 5 ml vial (5 ml fill), 30 ml vial (30 ml fill) and 10 mg/ml in 10 ml vials (10ml fill). The suitability of the packaging material has been shown. This includes integrity testing by liquid immersion microbial challenge. There are no overages in the drug product. Overfill of the vials has been described.

Formulation development has been very briefly described. The drug product has been originally developed for another market

Neither a production nor a stability overage is used.
The European reference product, Fortecortin (Merck Serono), is not preserved. The resulting generic product is preserved with a combination preservatives. No justification for the inclusion of preservatives in Dexamethasone Taw has been presented. Dexamethasone Taw 4 mg/ml and 10 mg/ml solution for injection/infusion is a single use product, see SPC where it is described under 4.2 "… The content of the vial is intended for single withdrawal. …" The inclusion of antimicrobial preservatives is not considered acceptable for single use preparations. Reference is made to the GL on excipients where it is stated inclusion of antimicrobial preservatives or should be avoided wherever possible. The finished product should be reformulated without preservatives (**MO**).

The inclusion of parabens and their esters in finished products for parenteral use requires the inclusion of the following information in the package leaflet and SPC: "May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm." This considered of importance for the inclusion of the COVID-19 indication and also for the paediatric population.

Filter and equipment compatibility has been investigated during pharmaceutical development. The pH of the drug product has been optimised with regard to product stability.

The finished product is manufactured under subdue light and headspace to be flushed with nitrogen after each ingredient mixing activity due to sensitivity to light and oxidation. It is manufactured by preparation of a solution of drug substance and excipients in water for injection followed by sterile filtration. Aseptic manufacturing is based on prior knowledge of thermal instability of dexamethasone, which excludes terminally sterilisation by heat treatment. Justification for the aseptic manufacturing process is requested (**OC**).

Compatibility with 0.9% Sodium chloride injection and 5% Dextrose injection has been shown.

The packaging material (amber glass vial (type 1), bromobutyl rubber stopper and aluminium seal with flip-off cap) is standard for the formulation type and was demonstrated through stability studies to provide adequate protection of the product during storage.

Manufacture of the product and process controls

Valid manufacturing licenses have been presented for sites in the EU. No valid GMP certificate has been provided for the manufacturing site in India. A valid GMP certificate for that manufacturer should be provided (**MO**).

The manufacturing process is non-standard. Active substance and excipients are dissolved in water for injections under light and oxygen protection, after each ingredient mixing activity. The manufactured bulk solution is filtered through sterilised sterilisation grade filters into presterilised vials. Filled vials are closed with rubber stoppers and sealed with aluminium flip-off caps. The manufacturing process should be described more detailed (**OC**) and in-process controls should be updated to describe all tests performed (**OC**). The limit for bioburden should be tested prior to the first filtration step (**OC**). Batch sizes have been clearly defined. The manufacturing process has been validated on the production scale batches – however differences between theoretical number of vials for each batch size and number of filled vials have been noted and should be explained (**OC**).

Bulk solution hold time data have been presented The proposed holding time is supported.

Process validation data have been submitted. Media fill summary reports have been presented.

Product specification, analytical procedures, batch analysis

The proposed release and shelf life specifications for Dexamethasone sodium phosphate 4 mg/ml and 10 mg/ml solution for injection/infusion are presented in the table below.

The finished product release and shelf-life specifications includes tests for: description (visual), identification (HPLC, TLC), pH (Ph. Eur.), light transmission at 650 nm, colour value at 430 nm, extractable volume (Ph. Eur.), osmolality (Ph. Eur.), particulate contamination (sub-visible and visible particles) (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), related substances (HPLC), preservative content (HPLC) and assay (HPLC).

Generally, the drug product specification covers all required parameters. Method description including validation reports are considered sufficient. In case the use of preservatives is justified the upper release limit should be narrowed The summary for the ICH Q3D risk assessment could not be found in the dossier and should be submitted (**OC**). The potential presence of nitrosamine impurities in Dexamethasone sodium phosphate injection manufactured by Mylan laboratories Ltd, SFF, Bangalore, India has been evaluated in line with the request included in the document EMA/409815/2020. The documentation provided is acceptable and the conclusion of the risk evaluation is endorsed. The description of the analytical procedures and their validation results are acceptable apart from the reported values for LOD and LOQ, which should be corrected (**OC**).

Batch analyses have been presented. All results are well within specifications. All the commercial formulation batches comply with the specification. The results indicate consistency and uniformity of the product, and that the process is under control.

The specification has been justified according to Ph.Eur. requirements for parenteral preparations, ICHQ6A (CPMP/ICH/367/96), ICH Q3B (CPMP/ICH/2738/99) and the monograph for the drug product "Dexamethasone Sodium Phosphate Injection" of the British Pharmacopoeia (current edition).

Adequate information has been provided for reference standards and materials. However EPCRS should be used when available (**OC**). Batch analysis data has been presented for batches of the proposed batch sizes and the results show consistency. The container closure system complies with relevant pharmacopoeia criteria.

Stability of the product

The claimed shelf life is 18 months stored below 25°C protected from light. Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at 25°C. Photostability testing was performed according to ICH Q1B.

Stability data (6 months) at the accelerated condition shows out of specification results for related substances. Related substances are within specification for the first three months of storage at accelerated storage conditions. No stability results at intermediate storage conditions have been presented (**OC**). The shelf-life at long term storage conditions for the 4 mg/ml strength is different for the three presentations (1ml, and 5 ml fill 18 months versus 30 ml fill 24 months). A discussion if these results was requested (**OC**). The conclusion regarding shelf-life in module 3 is different from the proposed shelf life in the SPC for 4mg/ml strength (30ml fill) and 10mg/ml strength. The documented shelf life at long term storage conditions is 24 months vs proposed shelf life in the SPC of 18 months. Unnecessary restrictions for the shelf life are not considered acceptable (**OC**). Photostability data have been provided for product stored in the original packaging. However, it should be discussed whether the diluted product should be stored protected from light (**OC**).

Post approval change management protocol(s)

Not applicable

Adventitious agents

Not applicable

GMO

Not applicable

2.1.2. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Active substance

Information on controls for the active substance is generally considered acceptable.

Finished medicinal product

The finished product is a single dose formulation consisting of two strengths (4mg/ml: 10mg/ml). All the ingredients comply with relevant standards.

Only limited details related to formulation development have been presented. Reference is made to the generic development related to an originator in the US, Decadron solution for injection/infusion by Merck. The European reference product is Fortecortin solution for injection/infusion by Merck Serono. The proposed finished product is preserved with preservatives ethyl- and propyl hydroxybenzoates, which is not acceptable for single use products. A major objection is raised, requesting reformulation of the finished product without preservatives (**MO**).

The manufacturing process of the finished product is non-standard. It is manufactured aseptically including sterilising filtration due to thermal instability of the active substance. The manufacturing process has been mainly satisfactory described. However, more details (such as process parameter settings, in-process controls and processing times) are requested. Process validation data including hold time validation and media fill have been presented.

The finished product manufacturer has not been inspected by EU authorities after September 2012 and no GMP certificate has been submitted. A request for inspection action prior to authorisation has been raised. The other manufacturers involved are appropriately authorised and acceptable. The lack of a valid GMP certificate for the manufacturing site Mylan Laboratories Limited, India is addressed in a major objection (**MO**).

Information on control of the finished medicinal product is generally considered acceptable. However, there are some issues that needs to be addressed, such as summary of the risk assessment on the elemental impurities, along with supportive analytical data. Clarification is requested regarding the analytical validation of LOD and LOQ.

The finished product is packaged amber glass vial (type 1) closed with a (bromobutyl) rubber stopper and aluminium seal with flip-off cap, which is normal for the type of formulation.

Stability has been studied in the proposed packaging at ICH long term and accelerated storage conditions. ICH Photostability and in-use stability has been tested. Stability testing lack studies at intermediate storage conditions, which should be provided in order to be able to set correct storage conditions. The presented stability data cover the proposed shelf life in the SPC. However, clarification

regarding different shelf-life conclusion in P.8 and the proposed shelf life in the SPC has been requested.

2.2. Non clinical aspects

As dexamethasone is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Dexamethasone Taw is claimed similar to the reference product in terms of qualitative and quantitative composition of the active substance, and similar inactive excipients.

2.2.1. Pharmacology

Primary pharmacodynamics

Dexamethasone is a potent, mono-fluorinated glucocorticoid with anti-allergic, anti-inflammatory, immunosuppressive, and anti-proliferative effects. Dexamethasone is approximately 7.5 times more potent than prednisolone and prednisone, and 25-30 times more potent than hydrocortisone, but without mineralocorticoid effects.

Glucocorticoids, such as dexamethasone, exert their biological effects by activating the transcription of corticosteroid-sensitive genes. The anti-inflammatory, immunosuppressive and anti-proliferative effects are caused by decreased formation, release and activity of inflammatory mediators, by the inhibition of specific functions and migration of inflammatory cells. In addition, the effect of sensitised T lymphocytes and macrophages on target cells may be prevented by corticosteroids.

Secondary pharmacology and safety pharmacology

Specific non-clinical secondary pharmacodynamic studies with dexamethasone were not identified in the literature. Dexamethasone act on cytoplasmic steroid receptors at extraordinarily low concentrations (e.g. lower nanomolar). Multiple cytoplasmic steroid receptors exist which are structurally similar and, therefore, there is a potential for cross-reactivity to off-target receptors.

Specific nonclinical safety pharmacology studies with dexamethasone have not been identified.

The Applicant has not provided any non-clinical data to address potential pharmacodynamic drug interactions. See Rapporteur's Clinical AR for further assessment of interactions.

2.2.2. Pharmacokinetics

Absorption

Dexamethasone sodium phosphate is rapidly hydrolysed in plasma to dexamethasone.

Following intramuscular administration of dexamethasone alcohol or dexamethasone 21-isonicotinate to dogs, C_{max} is reached within 30-40 minutes and the elimination half-life is 120-140 minutes.

Assuming an elimination half-life of 190 minutes in humans, the PK properties with regard to T_{max} and elimination half-lives of dexamethasone appears similar in dogs and humans.

Distribution

In the human circulation, small amounts of dexamethasone are bound to plasma proteins, mainly albumin. The binding of dexamethasone to proteins in rat, dog, cow, and human plasma was studied in

vitro by an equilibrium dialysis technique. Approximately 85, 73, 74, and 77% was bound in rat, dog, cow, and human plasma, respectively, in a concentration independent manner.

Metabolism

Hydroxylation of dexamethasone by cytochrome P450 3A4 was comparable in liver microsomes from Cynomolgus monkey and human. No parent compound could be detected in the urine of patients after oral administration of a small dose of dexamethasone (<4 mg/day) for a few weeks. However, 60% was recovered as 6-β-hydroxy-dexamethasone and 5-10% as 6-β-hydroxy-20-dihydrodexamethasone.

Excretion

Excretion in rats is mainly via metabolites in urine and faeces.

Pharmacokinetic drug interactions

Dexamethasone is a known substrate and inducer of CYP3A4. Dexamethasone has been shown to increase paracetamol hepatotoxicity in mice by decreasing liver glutathione levels and increasing the activation of paracetamol to a cytotoxic metabolite. With reference to the SmPC for Dexamethasone Phosphate Krka, potential interactions includes oestrogens (the half-life of glucocorticoids may be prolonged), medicines that induce CYP3A4 (the effect of corticoids may be reduced), CYP3A4 inhibitors (can reduce dexamethasone clearance), and ephedrine (the metabolism of glucocorticoids may be accelerated).

2.2.3. Toxicology

In accordance with Article 10(3) of Directive 2001/83/EC, a literature-based summary of the toxicological properties of dexamethasone is provided. The references comprises single and repeat-dose toxicity, genotoxicity, reproduction toxicity and endocrine toxicity.

Single and repeat-dose toxicity

Acute toxicity data was limited to an intraperitoneal LD50 of dexamethasone in mouse of 577 mg/kg, indicating low acute toxicity.

The repeat-dose toxicity studies comprises subcutaneous and oral dosing in rats, and intramuscular and oral dosing in dogs. Adverse findings in rats and dogs following repeated dosing for up to 26 weeks included thymus atrophy, decreased adrenal weight, hepatic findings (increased weight, increased glycogen), increased total cholesterol, and serum lipids. The findings are considered reversible. NOAELs were not determined. In both rats and dogs, dosing for 26 weeks led to deaths due to infections.

Genotoxicity

Dexamethasone was negative in Ames test and mouse lymphoma assay *in vitro*, and in micronucleus test *in vivo*.

Carcinogenicity

Carcinogenicity studies have not been provided.

Reproduction toxicity

Information on effects of dexamethasone on fertility was not found in the literature.

Findings in embryo-foetal development studies includes foetal thymus hypoplasia, increased incidence of cleft palate and other skeletal malformations/variations in mice, rats and rabbits. Further, experimental studies indicate effects on skeletal growth and reduced immune response in offspring

following exposure during gestation. Following exposure to dexamethasone late in pregnancy or early postnatal period, findings included reduced body weight and brain weight gain, reduced longitudinal bone growth, and effects on the pituitary/adrenal axis.

Impurities

The listed impurities in Dexamethasone Taw are considered within monographs or below limits of qualification.

2.2.4. Ecotoxicity/environmental risk assessment

A justification for not performing an environmental risk assessment was provided.

The Applicant justifies the lack of an ERA by arguing that the reference product and multiple generic products have already been marketed for several years. A significant increase in dexamethasone environmental burden is not envisaged with an additional COVID-19 indication, due to the short anticipated treatment duration.

2.2.5. Discussion on non-clinical aspects

The Applicant claims that Dexamethasone Taw is similar to the reference product Fortecortin with regard to qualitative and quantitative composition of the active substance, and similar inactive excipients. However, in contrast to Fortecortin, Dexamethasone Taw also contains methylparaben and propylparaben, leading to a Quality MO.

Pharmacology

Except for COVID-19, all other indications are in line with the approved indications for Fortecortin Inject. The new COVID-19 indication has not been addressed by the Applicant. However, in parallel with assessment of the current MAA, CHMP has completed an Article 5(3) referral, endorsing the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation. Thus, the lack of specific pharmacodynamic data supporting the new COVID-19 indication is considered acceptable.

The lack of secondary and safety pharmacology data on dexamethasone is acceptable, in view of the well-known clinical safety profile. Glucocorticoids are generally not considered arrythmogenic, and QT prolongation is not expected.

Pharmacokinetics

According to the non-clinical overview, small amounts of dexamethasone are bound to plasma proteins in the human circulation. Further, according to the proposed SmPC section 5.2, dexamethasone binds to plasma albumins in a dose-dependent manner, with the largest portion unbound at very high doses. This is in contrast to the *in vitro* findings summarised in the non-clinical overview, where a *concentration independent* protein binding of 85, 73, 74, and 77% was reported in rat, dog, cow, and human plasma, respectively (Peets et al, 1969). The applicant should clarify whether the publication by Peets et al is a valid data source regarding plasma protein binding in animals, considering the apparent incorrect human data **(OC)**.

The Applicant has not provided any information regarding tissue distribution for dexamethasone. Publicly available literature data does however exist (e.g. Mizushima et al, 1982). The Applicant is requested to update the Overview to include such data **(OC)**.

The metabolism in the species used in toxicity studies should be identified, in order to clarify if there are human specific metabolites, or if the animal species used in toxicity studied are considered metabolically relevant. For Dexamethasone Taw, data have only been provided for Cynomolgus

monkeys. It is however noted that in a study by Thomlinson et al (1997), the metabolism of dexamethasone was examined in microsomes from mouse, rat, hamster, guinea pig and rabbit, and compared with human microsomes. Considerable inter-species variation, both qualitative and quantitative, was observed, but the main human metabolite 6-hydroxydexamethasone (comprising 26%) was identified in all species (6, 17, 47, 19 and 10% in microsomes from mouse, rat, hamster, rabbit and guinea pig, respectively). Taken together, it can be concluded that the most important human metabolite is not human specific.

Limited data from rats indicate excretion via urine and faeces. This is in contrast to humans, where excretion mainly is in urine only. The observed difference between rats and humans could be related to differences in formation of water-soluble conjugates.

Excretion in milk has not been addressed. Other glucocorticoids are excreted in milk and, based on molecular weight, excretion of dexamethasone into milk should be expected (Briggs et al, 2015). This is adequately reflected in the proposed SmPC.

Toxicology

The Applicant's overview of repeat-dose toxicity studies is based on a literature summary by Van Leeuwen (Van Leeuwen, 1994) briefly referring to unpublished data. The study designs are not in accordance with current regulations, lacking toxicokinetic data and information on vehicle and dexamethasone form (e.g. dexamethasone base or salt). As indicated by the Applicant, this could have an impact on the interpretation of doses administered. For example, the molecular weight of dexamethasone sodium phosphate (516.4 g/ml) is >30% higher than for dexamethasone base (392.5 g/ml). These deficiencies are however considered acceptable, in view of the well-known clinical safety profile of dexamethasone.

The conclusion that dexamethasone is devoid of genotoxic potential is based on the literature summary by Van Leeuwen (Van Leeuwen, 1994), referring to unpublished data. Thus, the validity of the negative findings cannot be assessed. However, based on available literature from other studies and approved SmPC's for other marketed products, dexamethasone is considered without genotoxic potential.

Considering that dexamethasone has been marketed since 1959 without any carcinogenic concern, and in view of no genotoxic potential, the lack of non-clinical information with regard to carcinogenicity is considered acceptable.

According to the Applicant, information regarding effects of dexamethasone on fertility could not be found. This appears to be incorrect, as a search e.g. in PubMed reveals several publications. The Applicant is therefore requested to provide an updated Overview and Module 4 to include references and assessment of potential effects on fertility. Further, SmPC section 4.6 must be updated accordingly and in line with latest QRD-template **(OC)**.

Appropriate information with regard to use during pregnancy and breastfeeding is included in the proposed SmPC section 4.6.

Environmental Risk Assessment

Available data do not allow to conclude definitively on the potential risk of dexamethasone to the environment.

Without providing any supporting data, the Applicant claims that an increase in dexamethasone environmental burden is not envisaged with the additional COVID-19 indication. This approach is not in line with current guidance, and is not acceptable. An ERA has to be provided. According to the Q&A document (EMA/CHMP/SWP/44609/2010 Rev. 1), the ERA may consist of an adequate justification for the absence of specific study data. For Dexamethasone Taw, this could be by providing data supporting

that the COVID-19 indication will not lead to a significant increase of the Predicted Environmental Concentration (PEC) resulting from all approved indications for dexamethasone **(OC)**.

In case lack of studies cannot be justified, the applicant is asked to perform an ERA with tailored ecotoxicity assessment for the active substance dexamethasone taking into account the endocrine mode of action, e.g. by submission of a fish full life cycle test instead of the standard OECD 211 ELS test study or equivalent acceptable literature. For dexamethasone acceptable literature (LaLone et al. al (2012), Environ Toxicol Chem. 31(3):611-22) is available. Alternatively, it might be possible to get permission to use the ERA from other marketing authorisation holders by gaining a letter of consent from the respective owner. **(OC)**

2.2.6. Conclusion on non-clinical aspects

As dexamethasone is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

In general, the Overview is considered acceptable. In some aspects, however, updates are required. This is reflected by Other Concerns related to need for clarification on plasma protein binding, and missing data on tissue distribution and fertility.

Further, the Applicant is requested to submit an Environmental Risk Assessment for dexamethasone.

Provided that the questions are adequately answered, Dexamethasone Taw may be granted a marketing authorisation from a non-clinical point of view.

2.2.7. Clinical aspects

No clinical studies were conducted.

2.2.8. Pharmacokinetics

Introduction

This is an abridged application pursuant to article 10 of Directive 2001/83/EC, as amended, for Dexamethasone sodium phosphate 4 mg/mL and 10 mg/mL solution for intravenous (IV) injection/infusion referring to reference medicinal product, "Fortecortin", which is approved in Europe. The proposed product includes an additional therapeutic indication 'treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation)'. The proposed dose for this indication is 6 mg IV once daily for up to 10 days.

No clinical pharmacokinetic studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases. Pharmacological standard texts were also used.

Absorption

Following IV administration, peak serum levels are reached within ten minutes (Varis 2000).

A bioequivalence study was not conducted. The proposed product, dexamethasone sodium phosphate 4 mg/mL and 10 mg/mL solution for injection/infusion, is an aqueous IV solution containing the same the same active substance in the same concentration and similar excipients as the reference product (Fortecortin).

Distribution

Dexamethasone is widely distributed in the organism with a degree of plasma protein binding of 70%. It is distributed into several tissues, including the eyes (aqueous humour, cornea, iris, choroid, ciliary body, retina), breast milk and crosses the placental barrier (US. National Library for Medicine 2014). The volume of distribution is 2.0 L/kg (SmPC Dexamethasone Kern Pharma s.d.).

Elimination

Dexamethasone is a long-acting corticord, since its effects are maintained for up to 24 hours. Its total clearance varies between 2.8 and 3.5 mg/minute/kg, elimination half-life is 3-4 hours and its biological half-life is 36-54 hours (SmPC Dexamethasone Kern Pharma).

- **Excretion**

Dexamethasone is excreted in urine and faeces. About 9 to 10% of the dose is excreted as unchanged dexamethasone in the urine, with glucuronides present in small amounts (Varis 2000). After an intravenous dose of radiolabelled dexamethasone, mean recovery of urinary radioactivity at 24 h was 64% and unconjugated metabolites formed the largest fraction, 31% of the dose (Haque et al 1972).

- **Metabolism**

Dexamethasone undergoes hepatic metabolism as a cytochrome P450 3A4 substrate. It is mainly metabolized to 6-beta-hydroxydexamethasone. Other metabolites are also formed (e.g. 6-beta-hydroxy-20-dihydrodexamethasone).

Dexamethasone sodium phosphate is a prodrug. After intravenous administration, the hydrolysis of the phosphate ester to dexamethasone is rapid, with a half-life of 5 min. Conversion of dexamethasone phosphate to dexamethasone alcohol appears to be about 90% (Varis 2000).

Pharmacokinetics in the target population

No data on the PK of dexamethasone in the target population (hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO) were provided.

Section 4.2 of the proposed SmPC states that the dexamethasone dose for the management of COVID-19 is 6 mg IV once daily for up to 10 days. This is consistent with the dose used in the RECOVERY trial, where patients randomised to dexamethasone were administered a dose of 6 mg once per day (orally or IV) for up to 10 days. The median duration of treatment was 6 days.

Dexamethasone was chosen over other corticosteroids for COVID-19 treatment because it has a longer half-life and will auto taper when discontinued (Selvaraj et al 2020). After short-term administration of dexamethasone (e.g. less than 14 days) the HPA-axis is not suppressed. Therefore, treatment may be discontinued abruptly without expectation of adverse events (Kounta & Clark, 1997; Szabo & Winkler 1995).

Special populations

The RECOVERY trial included a heterogeneous study population of hospitalized patients in the United Kingdom with COVID-19.

- **Impaired renal function**

The proposed SmPC states that renal dysfunction does not substantially affect the elimination of dexamethasone.

In the RECOVERY trial, 8% of patients randomised to dexamethasone had severe renal impairment (n=168 patients with severe renal impairment).

- **Impaired hepatic function**

The proposed SmPC states that the elimination half-life is prolonged in severe liver disease and that in liver cirrhosis low doses may be sufficient or a dose reduction may be necessary.

In the RECOVERY trial, 2% of subjects randomised to dexamethasone had severe hepatic impairment (n=42 subjects with severe hepatic impairment).

- **Elderly**

The proposed SmPC states that because elderly patients are at an increased risk of osteoporosis, the benefit-risk balance of treatment with dexamethasone should be carefully weighed.

In the RECOVERY trial, the mean age of the participants randomised to dexamethasone was 66.1 years; 54% were <70 years, 22% were ≥70 and <80 years, and 24% were ≥80 years.

The FDA prescribing information for Dexamethasone (Drugs.com s.d.) states that there is not enough evidence concerning the efficiency and safety of dexamethasone in elderly patients above the age of 65. There is no clinical evidence concerning differences in outcomes between younger and elderly patients in relation to treatment with dexamethasone. However, because renal, hepatic, respiratory and cardiac functions can be impaired in the elderly and especially because concomitant diseases may be present resulting in use of pharmaceuticals, it is recommended to use the lowest dose possible. Caution is especially recommended in the presence of diabetes mellitus, fluid retention and hypertension.

Interactions

Dexamethasone is a substrate of CYP3A4 and a moderate inducer of this enzyme. Thus, several drug-drug interactions are expected.

Coadministration of remdesivir and dexamethasone has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Remdesivir is a prodrug predominantly metabolised by hydrolase, with some involvement (in vitro) of CYPs 2C8, 2D6 and 3A4, and is transported by P-gp. Dexamethasone is a moderate inducer of CYP3A4 and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio and is used for a short duration in the treatment of COVID-19. Dexamethasone is a substrate of CYP3A4 and, although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after IV administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure. (University of Liverpool COVID-19 Drug Interactions). Coadministration with remdesivir is allowable (Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance).

Aminoglutethimide may diminish adrenal suppression by corticosteroids.

Exposure relevant for safety evaluation

The patients in RECOVERY received the dose regimen as proposed by the applicant for the new COVID-19 indication for use. Whilst PK data were not obtained, the exposures that occurred in this heterogeneous study population were likely very representative of what would be expected in routine use if the new indication is approved.

2.2.9. Pharmacodynamics

No clinical pharmacodynamic studies on the proposed medicinal product (Dexamethasone sodium phosphate solution for injection/infusion) have been conducted. Instead, relevant data were provided based on published information on dexamethasone.

Mechanism of action

Dexamethasone, a synthetic glucocorticoid, has anti-inflammatory and immunosuppressive properties (Selvaraj et al. 2020).

Dexamethasone's therapeutic effects as an anti-inflammatory agent are, in general, attributed to the suppression of multiple mechanisms and pathways involved in the inflammatory response, leading to a decrease in pro-inflammatory chemical mediator levels at injury site (Menezes Carneiro, et al. 2014).

Dexamethasone's immunosuppressive action results from its ability to inhibit normal protein synthesis and stabilization of cell membranes, which leads to inhibition of cell activation and leukocyte degranulation (van Leeuwen s.d.) (Sauvage e Levy 2013) (US NLM - Toxnet s.d.).

Primary pharmacology

COVID-19 is associated with diffuse lung damage. Corticosteroids may modulate immune-mediated lung injury and reduce progression to respiratory failure and death (RECOVERY Collaborative group).

SARS-CoV-2 attaches to ACE2 receptors that are primarily located on type II pneumocytes. After infection, these cells release inflammatory signals that recruit macrophages, which in turn causes a "cytokine storm" that causes vasodilation, increased capillary permeability, and leucocyte migration. There is a release of Reactive Oxygen Species along with loss of surfactant, which causes the destruction of pneumocytes and the collapse of alveoli (Sriram et al. 2020; Shi et al. 2020). This, in turn, leads to Severe Inflammatory Response Syndrome and further progression to Severe Acute Respiratory Syndrome in severe cases (Selvaraj et al. 2020).

Early studies from China reported elevation of inflammatory markers including CRP, LDH, and IL-6 in patients with SARS-CoV-2. Elevated levels of CRP were associated with higher mortality, higher risk of clinical deterioration and progression of respiratory failure (Selvaraj et al. 2020).

2.2.10. Discussion on clinical pharmacology

Pharmacokinetics

This is an abridged application for Dexamethasone sodium phosphate 4 mg/mL and 10 mg/mL solution for injection/infusion referring to reference medicinal product, "Fortecortin", which is approved in Europe. The proposed product includes an additional therapeutic indication 'treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation)'.

It is agreed that a bioequivalence study is not required for this application. The product is an aqueous IV solution containing the same active substance in the same concentration as the currently approved product. Although the excipients in the test and reference formulations differ slightly, these differences will not affect the disposition of the drug substance.

The dossier reports a Tmax of 10 mins following IV administration of dexamethasone. The applicant should clarify if this refers to IV bolus injection or infusion. **(OC)**

The dossier reports an elimination half-life of 3-4 hours and a biological half-life of 36-54 hours. The applicant should clarify the difference between these two half-lives given that the values are markedly different. In addition, the applicant should clarify how the biological half-life was estimated. The SmPC should be amended to make it clearer what each half-life refers to. **(OC)**

Section 5.2 of the proposed SmPC states that dexamethasone is excreted predominantly through the kidney in the form of free dexamethasone alcohol and is partially metabolised. This is not consistent with what is reported in the dossier, which states that about 9 to 10% of the dose is excreted as

unchanged dexamethasone in the urine and that unconjugated metabolites form the largest fraction of dose recovered in the urine. The applicant is asked to clarify the elimination routes of dexamethasone and confirm that the information in the SmPC is accurate. **(OC)**

Section 4.2 of the proposed SmPC states that the dexamethasone dose for the management of COVID-19 is 6 mg IV once daily for up to 10 days, which is consistent with the dose used in the RECOVERY trial. For the treatment of COVID-19, the SmPC does not specify that the dexamethasone dose needs to be tapered when discontinued. This is considered acceptable given the short duration of dexamethasone treatment and its long duration of action.

In the RECOVERY trial, a small percentage of patients with severe renal or hepatic impairment and a reasonable number of elderly patients, including patients over 80 years of age, received dexamethasone at the recommended dose of 6 mg once daily and, although not specifically stated in the preliminary report, it seems that there were no dose adjustments.

Dexamethasone is a substrate and moderate inducer of CYP3A4. Thus, several drug-drug interactions are expected and detailed in the proposed SmPC. However, the SmPC does not include a statement that dexamethasone is a moderate CYP3A4 inducer and, therefore, may reduce the concentration and potential efficacy of concomitant medications that are sensitive CYP3A4 substrates with narrow therapeutic windows. In addition, the SmPC does not include a statement that aminoglutethimide may diminish adrenal suppression by corticosteroids. **(OC)**

In the dossier and proposed SmPC, the applicant reports the opinion of the University of Liverpool Drug Interactions Group, which considers that a clinically significant interaction between remdesivir and dexamethasone is unlikely given remdesivir's rapid clearance and moderate-high hepatic extraction ratio.

Pharmacodynamics

As this is an abridged application, no clinical pharmacodynamic studies on the proposed medicinal product were conducted and nor are they required. Relevant data were provided based on published information of dexamethasone.

Dexamethasone has been widely used for more than 50 years in the treatment of a variety of inflammatory conditions. In patients with pneumonia due to SARS-CoV-2, there is a hyper-inflammatory response. Therefore, the potential benefit of dexamethasone in the management of patients with severe COVID-19 is understandable.

2.2.11. Conclusions on clinical pharmacology

There are no major objections in terms of clinical pharmacology. There are a number of other concerns requiring further discussion from the applicant, some of which have implications for the SmPC.

2.2.12. Clinical efficacy

The legal basis of this submission is Article 10(3) hybrid application. The reference medicinal products Fortecortin were authorised in Germany in 1996 and 1979, respectively.

The applicant has not conducted any clinical studies to support this application but rather has performed a search of published information on dexamethasone revealed by data research in Medline and Embase databases. The applicant has selected publications up to year 2020 to replace clinical safety and efficacy studies.

Proposed indications:

Non COVID-19 indications

Systemic administration:

- cerebral oedema associated with cerebral tumour, neurosurgical procedures, cerebral abscess, bacterial meningitis (e.g. tuberculosis, typhoid, brucellosis)
- polytraumatic shock/prophylaxis of post-traumatic shock-lung syndrome
- severe, acute asthma attack
- initial parenteral treatment of extensive, acute, severe skin diseases like erythroderma, pemphigus vulgaris, acute eczema
- initial parenteral treatment of autoimmune diseases like systemic lupus erythematosus (especially visceral forms)
- active rheumatoid arthritis with a severe, progressive course, e.g. fast proceeding destructive forms and/or with extra-articular manifestations
- prophylaxis and treatment of post-operative or cytostatic-induced vomiting as part of anti- emetic regimens.

Local administration:

- intraarticular injection: persistent inflammation of one or a few joints after general management of chronic inflammatory joint diseases, activated osteoarthritis, acute forms of periarthropathia humeroscapularis
- infiltration therapy (when strictly indicated): non-bacterial tendovaginitis and bursitis, periarthropathy, insertional tendinopathy
- ophthalmology: subconjunctival administration in non-infectious keratoconjunctivitis, scleritis (except necrotising scleritis), uveitis anterior and intermedia.

COVID-19 indication

Together with the indications as approved in Germany for the reference medicinal product Fortecortin, the applicant seeks a new therapeutic indication for the use of Dexamethasone sodium phosphate Taw 4mg/ml and 10mg/ml that is not included in the reference medicinal product, Fortecortin. The additional proposed indication is as follows:

- treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation).

Dose-response studies and main clinical studies

Not applicable.

The study posology in the dexamethasone arm of the RECOVERY trial was either 6mg orally or intravenously for up to 10 days, or until discharge, if sooner.

Main study (ies)

Non COVID-19 indications

No clinical studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases.

The clinical overview refers to 46 publications up to year 2020.

The applicant's clinical overview document in section 2.5.4, the overview of clinical efficacy section, consists of 4 sections. These sections are entitled anti-neoplastic, anti-inflammatory, in the treatment of COVID and others.

In the efficacy section the applicant presented studies which investigated the efficacy of dexamethasone in the following conditions: multiple myeloma, acute lymphocytic leukaemia, patients recovering from surgery, in cardiac surgery and inflammatory neuropathy. In addition, some publications were provided regarding the use of chemotherapy-induced nausea and vomiting, patients with brain tumours or for the treatment in preterm infants.

The applicant provided English translation of the SmPC of the reference product (i.e Fortecortin Inject) and in the table below the indications of the reference product are compared with the proposed indications.

Fortecortin Inject indications	**Dexamethasone Taw indications**
Fortecortin Inject 40/100 mg	**All formulations**
Brain oedema triggered by brain neoplasm	
Polytraumatic shock/prophylaxis for post-traumatic acute respiratory distress syndrome	Polytraumatic shock/prophylaxis of post-traumatic shock-lung syndrome
Anaphylactic shock (after an epinephrine injection first)	
Fortecortin Inject 4/8 mg	
Brain oedema triggered by brain neoplasm, neurosurgery interventions, brain abscess, bacterial meningitis	Cerebral oedema associated with cerebral tumour, neurosurgical procedures, cerebral abscess, bacterial meningitis (e.g. tuberculosis, typhoid, brucellosis)
Polytraumatic shock/prophylaxis for post-traumatic acute respiratory distress syndrome	polytraumatic shock/prophylaxis of post-traumatic shock-lung syndrome
Severe acute asthma	severe, acute asthma attack
Initial parenteral treatment for extensive acute severe skin diseases such as generalised exfoliative dermatitis, pemphigus vulgaris, acute eczema	Initial parenteral treatment of extensive, acute, severe skin diseases like erythroderma, pemphigus vulgaris, acute eczema
Initial parenteral treatment for autoimmune disorders such as systemic lupus erythematosus (visceral forms in particular)	Initial parenteral treatment of autoimmune diseases like systemic lupus erythematosus (especially visceral forms)
Active rheumatoid arthritis taking a severe, progressive course, e.g. forms that quickly lead to joint destruction and/or with extraarticular manifestations	Active rheumatoid arthritis with a severe, progressive course, e.g. fast proceeding destructive forms and/or with extra-articular manifestations
Severe infectious diseases with toxic states (e.g. tuberculosis, typhus, brucellosis) only with	-

simultaneous antiinfective therapy	
Palliative therapy for malignant tumours	
Prophylaxis and therapy for postoperative or cytostatic-induced vomiting as part of antiemetic regimes	Prophylaxis and treatment of post-operative or cytostatic-induced vomiting as part of anti- emetic regimens.
Intraarticular injections: persistent inflammation in one or a small number of joints following general treatment of chronic inflammatory joint disorders, active osteoarthritis, acute forms of periarthritis humeroscapularis	Intraarticular injection: persistent inflammation of one or a few joints after general management of chronic inflammatory joint diseases, activated osteoarthritis, acute forms of periarthropathia humeroscapularis
Infiltration therapy (strictly defined indication): non-bacterial tenosynovitis and bursitis, periarthritis, enthesopathy	infiltration therapy (when strictly indicated): non-bacterial tendovaginitis and bursitis, periarthropathy, insertional tendinopathy
Ophthalmology (only Fortecortin Inject 4 mg): subconjunctival use for non-infectious keratitis, scleritis (with the exception of necrotising scleritis), iridocyclitis and intermediate uveitis	Ophthalmology: subconjunctival administration in non-infectious keratoconjunctivitis, scleritis (except necrotising scleritis), uveitis anterior and intermedia.

Posology

The following posology is presented in the SmPC:

Systemic administration:

- Cerebral oedema:

Adults: depending on the cause and severity, initial dose of 8 to 10 mg (up to 80 mg) IV, followed by 16 to 24 mg (up to 48 mg)/day IV, divided into 3 to 4 (6) individual doses for 4 to 8 days. A longer-term, lower-dose administration of dexamethasone may be required during irradiation and in the conservative treatment of inoperable brain tumours.

- Cerebral oedema due to bacterial meningitis: 0.15 mg/kg body weight every 6 hours for 4 days, children 0.4 mg/kg body weight every 12 hours for 2 days; starting before the first administration of the antibiotic. Severe cases, toxic states (e.g. tuberculosis, typhoid; only with concomitant anti-infective therapy): 4 to 20 mg/day IV, in single cases (e.g. typhoid) initially up to 200 mg.

Consideration should be given to official guidance for the resort to corticotherapy for the adequate management of infectious diseases.

- Post-traumatic shock/prophylaxis of post-traumatic shock-lung syndrome: initially 40 to 100 mg (children 40 mg) IV, a repeated dose after 12 hours or 16 to 40 mg every 6 hours for 2 to 3 days.

- Severe acute asthma attack: Adults: 8 to 20 mg IV as early as possible.

Children: 0.15 to 0.3 mg/kg body weight IV Doses should be repeated if necessary, based on the individual response and clinical need.

- Acute skin diseases: Depending on the nature and extent of the disease, daily doses of 8 to 40 mg IV, in severe cases up to 100 mg. Followed by treatment with decreasing doses.

- Active phases of rheumatic systemic diseases: systemic lupus erythematosus 6 to 16 mg/day.

- Active rheumatoid arthritis with a severe, progressive course: in rapidly destructive forms 12 to 16 mg/day, in extra-articular manifestations 6 to 12 mg/day.
- Prophylaxis and treatment of cytostatic-induced vomiting in anti-emetic regimens: 8 to 20 mg IV before starting chemotherapy, then 4 to 8 mg one to two times daily for 2 to 3 days as necessary (moderately emetogenic chemotherapy), or up to 3 to 4 days (highly emetogenic chemotherapy).
- Prophylaxis and treatment of post-operative vomiting: a single dose of 4 to 8 mg IV before the start of surgery; in children over 2 years of age: 0.15 mg/kg body weight (max. up to 8 mg).
- For the management of COVID-19, 6 mg IV, once a day for 10 days. Treatment should stop if discharged from hospital within the 10 days.

Local administration

Local infiltration and injection therapy is usually carried out with 4 to 8 mg; 2 mg of dexamethasone is sufficient if injected into small joints or administered by subconjunctival injection.

Some differences in posology as compared to the SmPC of the innovator product were reported for two indications i.e Prophylaxis and treatment of cytostatic-induced vomiting in anti-emetic regimens and Prophylaxis and treatment of post-operative vomiting. These differences are presented in the table below.

For other non COVID-19 indications, the posology is in line with the innovator product.

Fortecortin Inject Posology	**Dexamethasone Taw Posology**
Prophylaxis and therapy for cytostatic-induced vomiting as part of antiemetic regimes: 10–20 mg i.v. or orally before starting chemotherapy, then if required 2–3 times daily at 4–8 mg over 1–3 days (moderately emetogenic chemotherapy) or up to 6 days (highly emetogenic chemotherapy).	Prophylaxis and treatment of cytostatic-induced vomiting in anti-emetic regimens: 8 to 20 mg IV before starting chemotherapy, then 4 to 8 mg one to two times daily for 2 to 3 days as necessary (moderately emetogenic chemotherapy), or up to 3 to 4 days (highly emetogenic chemotherapy).
Prophylaxis and therapy for postoperative vomiting: individual dose of 8–20 mg i.v. beforesurgery starts, for children aged 2 years and over: 0.15–0.5 mg/kg body weight (max. 16 mg).	Prophylaxis and treatment of post-operative vomiting: a single dose of 4 to 8 mg IV before the start of surgery; in children over 2 years of age: 0.15 mg/kg body weight (max. up to 8 mg).

Methods

Trial design

This was a multi-centre, multi-arm, adaptive, open-label, randomised controlled trial with three possible stages of randomisation. In the main randomisation (Part A) patients are allocated to no additional treatment or one of 4 anti-viral or host-directed treatments.

These included:

- **Corticosteroid** in the form of dexamethasone**,** administered as an oral liquid or intravenous preparation 6 mg once daily for 10 days. In pregnancy, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead.
- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days.
- **Hydroxychloroquine** by mouth for 10 days (4 doses in first 24 hours and 1 dose every 12 hours for 9 days).
- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for a total of 10 days.

In addition, in a factorial design, eligible patients could also be randomly allocated simultaneously to no additional treatment or convalescent plasma (Part B).

Patients who deteriorate according to predefined criteria could be further randomised (Second randomisation) to no additional treatment or an immunomodulatory treatment (Tocilizumab).

- **Study participants**

Inclusion criteria:

Patients are eligible for the trial (Main randomisation) if all of the following are true:

- Hospitalised
- SARS-Cov-2 infection (clinically suspected or laboratory confirmed)
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.

Note:

Initially, recruitment was limited to patients aged at least 18 years but the age limit was removed from 9 May 20

For the second randomisation patients had to meet the following criteria:

- Randomised into the main RECOVERY trial no more than 21 days ago
- Clinical evidence of progressive COVID-19:

  - oxygen saturation <92% on room air or requiring oxygen (or in children, significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement); and

  - C-reactive protein (CRP) ≥75 mg/L

- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in this aspect of the RECOVERY trial

Exclusion criteria

If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining (or indicated) arms.

- **Treatments**

The study posology in the dexamethasone arm of the RECOVERY trial was either 6mg orally or intravenously for up to 10 days, or until discharge, if sooner.

- **Objectives**

Primary objective

To provide reliable estimates of the effect of study treatments on all-cause mortality within 28 days of randomisation.

Secondary objectives

To investigate the effect of study treatments on the duration of hospital stay, the need for (and duration of) ventilation, and the need for renal replacement therapy.

- **Outcomes/endpoints**

Primary outcome

Mortality (all-cause)

Secondary clinical outcomes

- Time to discharge from hospital
- Use of mechanical ventilation/Extra Corporal Membrane Oxygenation (ECMO) or death (among patients not on ventilation or ECMO at baseline)

- **Sample size**

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the COVID-19 pandemic. As the trial progressed, the trial Steering Committee, blinded to the results of the study treatment comparisons, formed the view that if 28-day mortality was 20% then a comparison of at least 2000 patients allocated to active drug and 4000 to usual care alone would yield at least 90% power at two-sided P=0.01 to detect a clinically relevant absolute difference of 4 percentage points between the two groups (a proportional reduction of one-fifth). Consequently, on 8 June 2020, the Steering Committee closed recruitment to the dexamethasone arm since enrolment exceeded 2000 patients.

- **Randomisation**

Eligible patients will be randomised using a 24/7 secure central web-based randomisation system, developed and hosted within NDPH, University of Oxford. Users of the system will have no insight into the next allocation, given that simple randomisation is being used. In the event that a patient is randomised inadvertently more than once during the same hospital admission, the first allocation will be used.

The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer, and the Steering Committee notified if an error in the randomisation process is identified.

Eligible and consenting patients were assigned in a ratio of 2:1 to either usual standard of care or to usual standard of care plus dexamethasone 6 mg once daily (oral or intravenous) for up to 10 days (or until discharge if sooner) or to one of the other suitable and available treatment arms using web-based simple randomization with allocation concealment. For some patients, dexamethasone was either unavailable at the hospital at the time of enrolment or considered by the managing doctor to be either definitely indicated or definitely contraindicated. These patients were excluded from entry in the randomized comparison of dexamethasone vs. usual care and hence are not part of this report. The randomly assigned treatment was prescribed by the treating clinician. Participants and local study staff were not blinded to the allocated treatment

- **Blinding (masking)**

This was an open-label study. However, while the study was in progress, access to tabular results of study outcomes by allocated treatment allocation was be available to the research team, patients, or members of the Steering Committee (unless the DMC advises otherwise).

- **Statistical methods**

For each pairwise comparison with the 'no additional treatment' arm, the primary objective was to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after first randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

The secondary objectives were to assess the effects of study treatments on duration of hospital stay; and, among patients not on mechanical ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO.

Other objectives included the assessment of the effects of study treatments on the need for any ventilation (and duration), renal replacement therapy and new major cardiac arrhythmias.

Study outcomes were assessed based on data recorded up to 28 days and up to 6 months after the main randomisation.

Data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital) and from relevant research studies (such as UK Biobank and Genomics England) allowed subsidiary analyses of the effect of the study treatments on particular non-fatal events (e.g. ascertained through linkage to Hospital Episode Statistics), the influence of pre-existing major co-morbidity (e.g. diabetes, heart disease, lung disease, hepatic insufficiency, severe depression, severe kidney impairment, immunosuppression), and longer-term outcomes as well as in particular sub-categories of patient (e.g. by genotype, pregnancy).

Methods of analysis

For all outcomes, comparisons were made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

For time-to-event analyses, each treatment group was compared with the no additional treatment group using the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) was used to estimate the average event rate ratio (and its confidence interval) for those allocated to each treatment group versus the no additional treatment group. For binary outcomes where the timing is unknown, the risk ratio and absolute risk difference was calculated with confidence intervals and p-value reported. For the primary outcome (death within 28 days of first randomisation), discharge alive before 28 days was assumed safety from the event (unless there is additional data confirming otherwise).

Pairwise comparisons within each randomisation were made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation phase A, main randomisation phase B, and second randomisation).

However, since not all treatments may be available or suitable for all patients, those in the no additional treatment arm were only be included in a given comparison if, at the point of their randomisation, they could alternatively have been randomised to the active treatment of interest. Allowance for multiple treatment comparisons due to the multi-arm design was made. All p-values will be 2-sided.

Pre-specified subgroup analysis (e.g., disease severity; time since onset of symptoms; sex; age group) was conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate).

Results

- **Participant flow**

Of the 11,320 patients randomized between 19 March and 8 June, 9355 (83%) were eligible to be randomized to dexamethasone (that is dexamethasone was available in the hospital at the time and the patient had no known indication for or contraindication to dexamethasone). Of these, 2104 were randomized to dexamethasone and 4321 were randomized to usual care, with the remainder being randomized to one of the other treatment arms.

- **Conduct of the study**

There were amendments the trial protocol.

Table 1: Amendments to the recovery trial protocol

Version number	Date	Brief Description of Changes
1.0	13-Mar-2020	Initial version
2.0	21-Mar-2020	Addition of hydroxychloroquine. Administrative changes and other clarifications.
3.0	07-Apr-2020	Extension of eligibility to those with suspected COVID-19 Addition of azithromycin arm. Addition of inclusion of adults who lack permanently lack capacity. Change to primary outcome from in-hospital death to death within 28 days of randomization.
4.0	14-Apr-2020	Addition of second randomisation to tocilizumab vs. standard of care among patients with progressive COVID-19.
5.0	24-Apr-2020	Addition of children to study population.
6.0	14-May-2020	Addition of convalescent plasma
7.0	18-Jun-2020	Allowance of randomisation in part B of main randomisation without part A. Removal of hydroxychloroquine and dexamethasone treatment arms.
8.0	03-Jul-2020	Removal of lopinavir-ritonavir Addition of intravenous immunoglobulin arm for children Changes to corticosteroid dosing for children. Addition of baseline serum sample in convalescent plasma randomisation

Assessor's comment

It is noted that on 07.04.2020 the primary endpoint was changed from in-hospital death to death within 28 days of randomisation.

- **Baseline data**

Mean age of study participants in this comparison was 66.1 years and 36% patients were female.

A history of diabetes was present in 24% of patients, heart disease in 27%, and chronic lung disease in 21%, with 56% having at least one major comorbidity recorded. In this analysis, 82% of patients had laboratory confirmed SARS-CoV-2 infection, with the result currently awaited for 9%. At randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.

Follow-up information was complete for 6119 (95%) of the randomized patients. Of those allocated to dexamethasone, 95% received at least 1 dose and the median number of days of treatment was 6 days. 7% of the usual care group received dexamethasone. Use of azithromycin during the follow-up period was similar in both arms (23% vs. 24%) and very few patients received hydroxychloroquine, lopinavir-ritonavir, or interleukin-6 antagonists during follow-up. Remdesivir only became available for use in the UK under the MHRA Emergency Access to Medicines Scheme on 26 May 2020.

Table 2: Baseline characteristics by randomized allocation and level of respiratory support received

	Treatment allocation		Respiratory support received at randomization		
	Dexamethasone (n=2104)	Usual care (n=4321)	No oxygen received (n=1535)	Oxygen only (n=3883)	Invasive mechanical ventilation (n=1007)
Age, years	66.9 (15.4)	65.8 (15.8)	69.3 (17.6)	66.7 (15.3)	59.0 (11.5)
<70	1142 (54%)	2506 (58%)	660 (43%)	2149 (55%)	839 (83%)
≥70 to <80	467 (22%)	860 (20%)	338 (22%)	837 (22%)	152 (15%)
≥80	495 (24%)	955 (22%)	537 (35%)	897 (23%)	16 (2%)
Sex					
Male	1338 (64%)	2750 (64%)	892 (58%)	2462 (63%)	734 (73%)
Female*	766 (36%)	1571 (36%)	643 (42%)	1421 (37%)	273 (27%)
Number of days since symptom onset	8 (5-13)	9 (5-13)	6 (3-10)	9 (5-12)	13 (8-18)
Respiratory support received					
No oxygen received	501 (24%)	1034 (24%)	1535 (100%)	0 (0%)	0 (0%)
Oxygen only	1279 (61%)	2604 (60%)	0 (0%)	3883 (100%)	0 (0%)
Invasive mechanical ventilation	324 (15%)	683 (16%)	0 (0%)	0 (0%)	1007 (100%)
Previous diseases					
Diabetes	521 (25%)	1025 (24%)	342 (22%)	950 (24%)	254 (25%)
Heart disease	586 (28%)	1171 (27%)	519 (34%)	1074 (28%)	164 (16%)
Chronic lung disease	415 (20%)	931 (22%)	351 (23%)	883 (23%)	112 (11%)
Tuberculosis	6 (<0.5%)	19 (<0.5%)	8 (1%)	11 (<0.5%)	6 (1%)
HIV	12 (1%)	20 (<0.5%)	5 (<0.5%)	21 (1%)	6 (1%)
Severe liver disease	37 (2%)	82 (2%)	32 (2%)	72 (2%)	15 (1%)
Severe kidney impairment	167 (8%)	358 (8%)	120 (8%)	253 (7%)	152 (15%)
Any of the above	1174 (56%)	2417 (56%)	911 (59%)	2175 (56%)	505 (50%)
SARS-Cov-2 test result					
Positive	1702 (81%)	3553 (82%)	1198 (78%)	3144 (81%)	913 (91%)
Negative	213 (10%)	397 (9%)	182 (12%)	398 (10%)	30 (3%)
Test result not yet known†	189 (9%)	371 (9%)	155 (10%)	341 (9%)	64 (6%)

Results are count (%), mean ± standard deviation, or median (inter-quartile range). * Includes 6 pregnant women. † SARS-Cov-2 test results are captured on the follow-up form, so are currently unknown for some. There was a significant (2p=0.008) difference in mean age between those allocated dexamethasone and those allocated usual care, but no significant differences between these groups in any other baseline characteristic. The 'oxygen only' group includes non-invasive ventilation.

- **Numbers analysed**

A preliminary analysis was performed on 6,425 participants, with 2,104 participants in the dexamethasone arm and 4,321 in the control arm.

- **Outcomes and estimation**

Primary Outcome

Significantly fewer patients allocated to dexamethasone met the primary outcome of 28-day mortality than in the usual care group (454 of 2104 patients [21.6%] allocated dexamethasone vs. 1065 of 4321 patients [24.6%] allocated usual care; rate ratio, 0.83; 95% confidence interval [CI], 0.74 to 0.92; P<0.001).

Table 3: Effect of allocation to dexamethasone on main study outcomes

	Treatment allocation			
	Dexamethasone (n=2104)	Usual care (n=4321)	RR (95% CI)	p-value
Primary outcome:				
28-day mortality	454 (21.6%)	1065 (24.6%)	0.83 (0.74-0.92)	<0.001
Secondary outcomes:				
Discharged from hospital within 28 days	1360 (64.6%)	2639 (61.1%)	1.11 (1.04-1.19)	0.002
Receipt of invasive mechanical ventilation or death*	425/1780 (23.9%)	939/3638 (25.8%)	0.91 (0.82-1.00)	0.049
Invasive mechanical ventilation	92/1780 (5.2%)	258/3638 (7.1%)	0.76 (0.61-0.96)	0.021
Death	360/1780 (20.2%)	787/3638 (21.6%)	0.91 (0.82-1.01)	0.07

RR=Rate Ratio for the outcomes of 28-day mortality and hospital discharge, and risk ratio for the outcome of receipt of invasive mechanical ventilation or death (and its subcomponents). Estimates of the RR and its 95% confidence interval are adjusted for age in three categories (<70 years , 70-79 years, and 80 years or older). * Analyses exclude those on invasive mechanical ventilation at randomization.

In a pre-specified subgroup analysis by level of respiratory support received at randomization, there was a significant trend showing the greatest absolute and proportional benefit among those patients receiving invasive mechanical ventilation at randomization (test for trend p<0.001).

Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002) (Figure 1B-C). However, there was no evidence of benefit among those patients who were not receiving respiratory support (rate ratio 1.22 [95% CI 0.93 to 1.61]; p=0.14) (Figure 1D). Sensitivity analyses without age adjustment produced similar findings.

Patients on invasive mechanical ventilation at randomization were on average 10 years younger than those not receiving any respiratory support and had symptoms prior to randomization for 7 days longer 28-day mortality in the usual care group was highest in those who were receiving invasive mechanical ventilation at randomization (40.7%), intermediate in those patients who received oxygen only (25.0%), and lowest among those who were not receiving respiratory support at randomization (13.2%). Consequently, the greatest absolute reductions in 28-day mortality were seen among those patients on invasive mechanical ventilation.

Patients with longer duration of symptoms (who were more likely to be on invasive mechanical ventilation at randomization) had a greater mortality benefit, such that dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with more recent symptom onset (test for trend p<0.001).

Figure 1: **Effect of allocation to dexamethasone on 28−day mortality by level of respiratory support received at randomization**

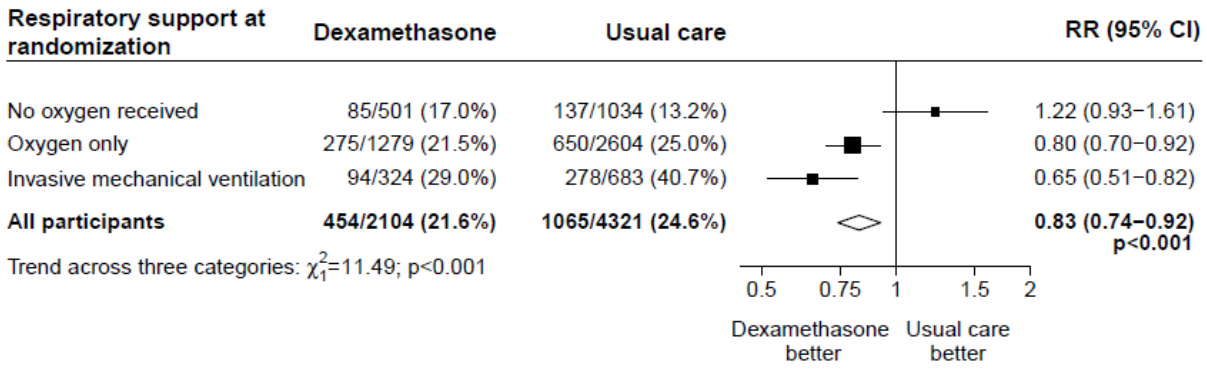
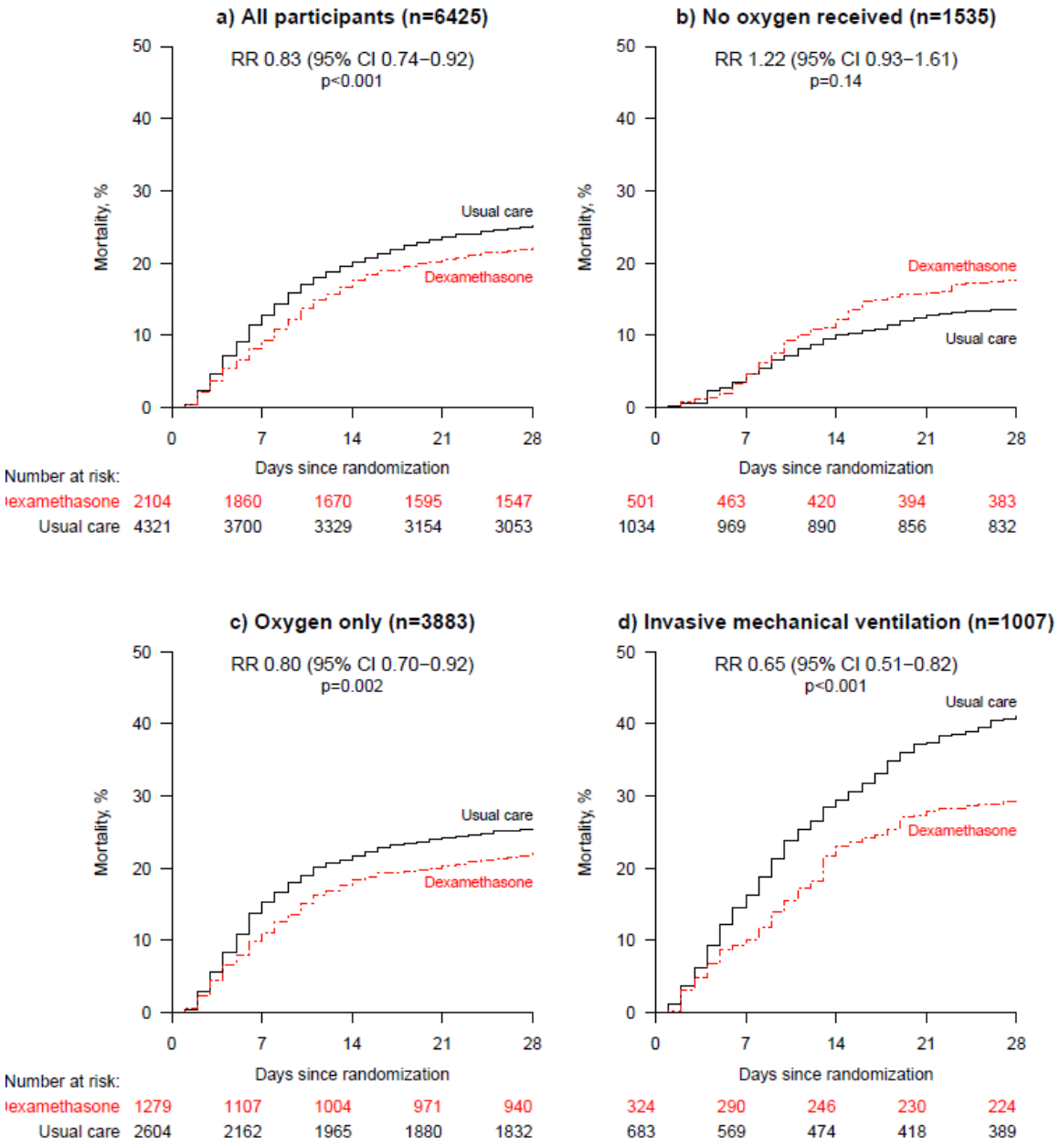


Figure 2: **28−day mortality in all patients (panel a) and separately according to level of respiratory support received at randomization (panels b−d)**



Secondary outcomes

Allocation to dexamethasone was associated with a shorter duration of hospitalization than usual care (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.11 [95% CI 1.04 to 1.19]; p=0.002) (Table 2) with the greatest effect seen among those receiving invasive mechanical ventilation at baseline (test for trend p=0.002)

Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower among those allocated to dexamethasone (risk ratio 0.91 [95% CI 0.82 to 1.00]; p=0.049) (Table 2) but with significantly greater effects among patients receiving oxygen at randomization (test for trend p=0.008).

Subsidiary clinical outcomes

The risk of progression to invasive mechanical ventilation was lower among those allocated dexamethasone vs. usual care (risk ratio 0.76 [95% CI 0.61 to 0.96]; p=0.021).

Preliminary analyses indicate no excess risk of any particular cause of death (in particular there was no excess of deaths due to non-COVID infection). More detailed analyses of cause-specific mortality, need for renal dialysis or hemofiltration, and duration of ventilation are in preparation.

Ancillary analyses

N/A

Summary of main efficacy results

Table 4: Summary of Efficacy for RECOVERY Trial

<table>
<tr><td colspan="3">Title: Randomised Evaluation of COVID-19 Therapy (RECOVERY)</td></tr>
<tr><td>Study identifier</td><td colspan="2">ClinicalTrials.gov number, NCT04381936;
ISRCTN number, 50189673</td></tr>
<tr><td></td><td colspan="2">RECOVERY is a randomised trial investigating whether treatment with either Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, Convalescent plasma or Tocilizumab prevents death in patients with COVID-19. In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARSCoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine. These groups also advised that other treatments will soon emerge that require evaluation. This is an interventional clinical trial with 15000 participants (including adults and children) with seven treatment groups with long duration of study. The study completion date is Dec 2031.
The randomization of patients to receive dexamethasone, hydroxychloroquine, or lopinavir–ritonavir has been stopped. The trial continues randomization to groups receiving azithromycin, tocilizumab, or convalescent plasma.
The published literature by Recovery collaborative Group in Jul 2020, reports the preliminary results of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial of dexamethasone in patients hospitalized with Covid-19.</td></tr>
<tr><td>Design</td><td colspan="2">Study Type: Interventional Clinical Trial
Estimated Enrollment: 6425 participants
Allocation: Randomised
Intervention Model: Factorial Assignment
Intervention Model Description: Eligible and consenting patients were assigned in a 2:1 ratio to receive either the usual standard of care alone or the usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days (or until hospital discharge if sooner) or to receive one of the other suitable and available treatments that were being evaluated in the trial.
Masking: Open label
Primary Purpose: To evaluate the effects of potential treatments (dexamethasone) in patients hospitalized with Covid-19.</td></tr>
<tr><td></td><td>Duration of main phase: 109 days
Duration of Run-in phase: Not applicable
Duration of Extension phase: Not applicable</td><td>Study Start date: First patient randomization date: March 19, 2020
Estimated Primary Completion date: Last patient randomization date: June 08, 2020
Estimated Study completion date: Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Exploratory:
Appropriate sample sizes could not be estimated when the trial was being planned at the start of the Covid-19 pandemic. As the trial progressed, the trial steering committee, whose members were unaware of the results of the trial</td></tr>
</table>

	comparisons, determined that if 28-day mortality was 20%, then the enrollment of at least 2000 patients in the dexamethasone group and 4000 in the usual care group would provide a power of at least 90% at a two-sided P value of 0.01 to detect a clinically relevant proportional reduction of 20% (an absolute difference of 4 percentage points) between the two groups..	
Treatments groups	Low dose corticosteroids	Drug: Dexamethasone administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days.
	No Intervention: Standard Care	Patient receives usual hospital care
Endpoints and definitions	Primary Outcome Measures:	All-cause mortality within 28 days after randomisation
	Secondary Outcome Measures:	Time until discharge from the hospital and, among patients not receiving invasive mechanical ventilation at the time of randomization, subsequent receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death.
	Other Outcome Measures:	Other prespecified clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation.
Database lock	July 06, 2020	

Results and Analysis

Disposition:

Of the 11,303 patients who underwent randomization from March 19 to June 8, 2020, a total of 9355 patients (83%) were eligible to receive dexamethasone (i.e., the drug was available in the hospital at the time and the patient had no known indication for or contraindication to dexamethasone). Of these patients, 6425 underwent randomization to receive either dexamethasone (2104 patients) or usual care alone (4321 patients).

Baseline Characteristics:

The mean (±SD) age of the patients in this comparison was 66.1±15.7 years, and 36% of the patients were female. A history of diabetes was present in 24% of the patients, heart disease in 27%, and chronic lung disease in 21%, with 56% having at least one major coexisting illness recorded. In this analysis, 89% of the patients had laboratory-confirmed SARS-CoV-2 infection, and 0.4% were currently awaiting the result. At randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.

Treatment Intervention:

The median duration of treatment was 7 days (interquartile range, 3 to 10). In the usual care group, 8% of the patients received dexamethasone as part of their clinical care. The use of azithromycin during the follow-up period was similar in the dexamethasone group and the usual care group (24% vs. 25%), and 0 to 3% of patients received hydroxychloroquine, lopinavir–ritonavir, or interleukin-6 antagonists during follow-up. After remdesivir became available in the United Kingdom on May 26, 2020, the drug was administered to 3 patients in the dexamethasone group and 2 patients in the usual care group.

Follow-up information for the primary outcome was complete for 6418 patients (99.9%) who had undergone randomization. In the dexamethasone group, 95% of the patients received at least one dose of the drug.

Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In a prespecified analysis according to the level of respiratory support that the patients were receiving at randomization, there was a trend showing the greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17). The greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization. Among the patients who were not receiving invasive mechanical ventilation at randomization, the number of patients who progressed to the prespecified composite secondary outcome of invasive mechanical ventilation or death was lower in the dexamethasone group than in the usual care group (risk ratio, 0.92; 95% CI, 0.84 to 1.01). This effect was greater among the patients who were receiving oxygen at randomization.			
Analysis description	Primary Analysis		
Analysis population and time point description	All analyses were performed according to the intention to-treat principle. For the primary outcome of 28-day mortality, the hazard ratio from Cox regression was used to estimate the mortality rate ratio. Among the few patients (0.1%) who had not been followed for 28 days by the time of the data cutoff on July 6, 2020, data were censored either on that date or on day 29 if the patient had already been discharged. That is, in the absence of any information to the contrary, these patients were assumed to have survived for 28 days. Kaplan–Meier survival curves were constructed to show cumulative mortality over the 28-day period. Cox regression was used to analyze the secondary outcome of hospital discharge within 28 days, with censoring of data on day 29 for patients who had died during hospitalization. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among patients who were not receiving invasive mechanical ventilation at randomization), the precise date of invasive mechanical ventilation was not available, so a log-binomial regression model was used to estimate the risk ratio.		
Descriptive statistics and estimate variability	Treatment group	Dexamethasone	Usual Care
	Number of subjects (N)	2014	4321
Primary outcome measure - Mortality at 28 days – All patients	Mortality at 28 days [n/N (%)]	482/2104 (22.9%)	1110/4321 (25.7%)
	Rate or Risk Ratio (95% CI)	0.83 (0.75 – 0.93)	
Primary outcome measure - Mortality at 28 days in patients – Patients receiving invasive ventilation at randomisation	Mortality at 28 days [n/N (%)]	95/324 (29.3)	283/683 (41.4)
	Rate or Risk Ratio (95% CI)	0.64 (0.51–0.81)	
Primary outcome measure - Mortality at 28 days in patients – Patients receiving oxygen only at randomisation	Mortality at 28 days [n/N (%)]	298/1279 (23.3)	682/2604 (26.2)
	Rate or Risk Ratio (95% CI)	0.82 (0.72–0.94)	
Primary outcome measure - Mortality at 28 days in patients – Patients receiving no oxygen at randomisation	Mortality at 28 days [n/N (%)]	89/501 (17.8)	145/1034 (14.0)
	Rate or Risk Ratio (95% CI)	1.19 (0.91–1.55)	
Secondary outcome measure – Discharged from hospital within 28 days	Discharged from hospital within 28 days [n/N (%)]	1413/2104 (67.2%)	2745/4321 (63.5%)
	Rate or Risk Ratio (95% CI)	1.10 (1.03–1.17)	
Secondary outcome measure – Patients progressed to receive	Invasive mechanical ventilation required or death [n/N (%)]	456/1780 (25.6%)	994/3638 (27.3%)

Invasive mechanical ventilation or death	Rate or Risk Ratio (95% CI)	0.92 (0.84–1.01)	
Secondary outcome – Patients progressed to receive Invasive mechanical ventilation	Invasive mechanical ventilation [n/N (%)]	102/1780 (5.7%)	285/3638 (7.8%)
	Rate or Risk Ratio (95% CI)	0.77 (0.62–0.95)	
Secondary Outcome – Patients who died	Death [n/N (%)]	387/1780 (21.7%)	827/3638 (22.7%)
	Rate or Risk Ratio (95% CI)	0.93 (0.84–1.03)	
Notes	The results show that among hospitalized patients with Covid-19, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality than usual care in patients who were receiving invasive mechanical ventilation at randomization (by 12.3 age-adjusted percentage points, a proportional reduction of approximately one third) and those who were receiving oxygen without invasive mechanical ventilation (by 4.1 age-adjusted percentage points, a proportional reduction of approximately one fifth). However, there was no evidence that dexamethasone provided any benefit among patients who were not receiving respiratory support at randomization, and the results were consistent with possible harm in this subgroup. The benefit was also clear in patients who were being treated more than 7 days after symptom onset, when inflammatory lung damage is likely to have been more common.		

Analysis performed across trials (pooled analyses and meta-analysis)

A recent meta-analysis has been published 'Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis' by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group in JAMA online (JAMA. doi:10.1001/jama.2020.17023; Published online September 2, 2020). This publication was not provided by the applicant.

Results

Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients).

The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events.

A total of 1703 patients (median age, 60 years [interquartile range, 52-68 years]; 488 [29%] women) were included in the analysis. Risk of bias was assessed as "low" for 6 of the 7 mortality results and as "some concerns" in 1 trial because of the randomization method. Five trials reported mortality at 28 days, 1 trial at 21 days, and 1 trial at 30 days. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; P < .001 based on a fixed-effect meta-analysis). There was little inconsistency between the trial results (I 2 = 15.6%; P = .31 for heterogeneity) and the summary OR was 0.70 (95% CI, 0.48-1.01; P = .053) based on the random-effects meta-analysis. The fixed-effect summary OR for the association with mortality was 0.64 (95% CI, 0.50-0.82; P < .001) for dexamethasone compared with usual care or placebo (3 trials, 1282 patients, and 527 deaths), the OR was 0.69 (95% CI, 0.43-1.12; P = .13) for hydrocortisone (3 trials, 374 patients, and 94 deaths), and the OR was 0.91 (95% CI, 0.29-2.87; P = .87) for methylprednisolone (1 trial, 47 patients, and 26 deaths). Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

The applicant provided the following additional publications for COVID-19 indications.

#	Title	Authors	Study Type	Results
1	Effect of Dexamethasone in Hospitalized Patients with COVID-19 Preliminary Report	RECOVERY Collaborative Group, 2020	Randomized, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual care in patients hospitalized with COVID-19.	Results discussed in the study report
2	Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective	Singh A. K. et al, 2020	Systematic review on the role of corticosteroid in the management of patients with COVID-19.	3.2. 'Studies with corticosteroid treatment in previous corona virus infections' • One meta-analysis showed a considerable higher mortality (Risk ratio [RR] 1.75; 95% confidence interval [CI], 1.30e2.36; p ¼ 0.0002) and higher rate of secondary infection (RR 1.98; 95% CI, 1.04e3.78; p ¼ 0.04) in steroid treated influenza patients [18]. Methylprednisolone was used in a significant number of studies followed by hydrocortisone, prednisolone and dexamethasone. Section 3.3.2 'Studies where corticosteroid was used to evaluate its outcome' • Of the 5 studies (4 retrospective and 1 quasi-prospective study) conducted with corticosteroids, 3 studies have shown a benefit, while 2 studies shown no benefit, and there was a suggestion of significant harm especially in the critical cases in one sub-study (propensity-matched adjusted hazard ratio [HR] 2.90; 95% CI, 1.17e7.16; p ¼ 0.021) [28-32].

				Discussion • Corticosteroid use in previous viral respiratory illnesses have also demonstrated a delayed viral clearance [9,10,17]. Similar results have been shown in convalescent COVID-19 patients as well [26].
3	Short-Term Dexamethasone in Sars-CoV-2 Patients	SELVARAJ V. et al, 2020	Case Series (21 patients with SARS-CoV-2 and treated with a short course of dexamethasone, alone or in addition to current investigative therapies).	**Results:** CRP levels decreased significantly following the start of dexamethasone from mean initial levels of 129.52 to 40.73 mg/L at time of discharge. 71% percent of the patients were discharged home with a mean length of stay of 7.8 days. None of the patients had escalation of care, leading to mechanical ventilation. Two patients were transferred to inpatient hospice facilities on account of persistent hypoxemia, in line with their documented goals of care. Conclusions: A short course of systemic corticosteroids among inpatients with SARS-CoV-2 with hypoxic respiratory failure was well tolerated, and most patients had improved outcomes. This limited case series may not offer concrete evidence towards the benefit of corticosteroids in COVID-19. However, patients' positive response to short-term corticosteroids demonstrates that they may help blunt the severity of inflammation and prevent a severe hyperinflammatory phase, in turn reducing the length of stay, ICU admissions, and healthcare costs.
4	Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial	Villar J., et al, 2020	Multicentre, randomised controlled trial in a network of 17 intensive care units (ICUs) in Spain (Between March 28, 2013, and Dec 31, 2018).	This trial was stopped by the data safety monitoring board due to low enrolment rate after enrolling more than 88% (277/314) of the planned sample size in December 2018. Between March 28, 2013, and Dec 31, 2018, we enrolled 277 patients and randomly assigned 139 patients to the dexamethasone group and 138 to the control group. The trial was stopped by the data safety monitoring board due to low enrolment rate after enrolling more than 88% (277/314) of the planned sample size. The mean number of ventilator-free days was higher in the dexamethasone group than in the control group (between-group difference 4·8 days [95% CI 2·57 to 7·03]; p<0·0001). At 60 days, 29 (21%) patients in the dexamethasone group and 50 (36%) patients in the control group had died (between-group difference −15·3% [−25·9 to −4·9]; p=0·0047). The proportion of adverse events did not differ significantly between the dexamethasone group and control group. The most common adverse events were hyperglycaemia in the ICU (105 [76%] patients in the dexamethasone group vs 97 [70%] patients in the control group), new infections in the ICU (eg, pneumonia

				or sepsis; 33 [24%] vs 35 [25%]) and barotrauma (14 [10%] vs 10 [7%]). Conclusion: Early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS.
5	The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis	Yang Z., et al, 2020	Systematic literature review and meta-analysis.	A total of 5270 patients from 15 studies were included in this meta-analysis. The result indicated that critical patients were more likely to require corticosteroids therapy (risk ratio [RR] = 1.56, 95% confidence interval [CI] = 1.28-1.90, P < 0.001). However, corticosteroid treatment was associated with higher mortality (RR = 2.11, 95%CI = 1.13-3.94, P = 0.019), longer length of stay (weighted mean difference [WMD] = 6.31, 95%CI = 5.26–7.37, P < 0.001), a higher rate of bacterial infection (RR = 2.08, 95%CI = 1.54–2.81, P < 0.001), and hypokalemia (RR = 2.21, 95%CI = 1.07–4.55, P = 0.032) but not hyperglycemia (RR = 1.37, 95%CI = 0.68–2.76, P = 0.376) or hypocalcemia (RR = 1.35, 95%CI = 0.77–2.37, P = 0.302). Conclusion: Patients with severe conditions are more likely to require corticosteroids. Corticosteroid use is associated with increased mortality in patients with coronavirus pneumonia.
6	Coronavirus Disease 2019 (COVID-19) Treatment Guidelines	NIH, 2020	Treatment guidelines	

2.2.13. Discussion on clinical efficacy

This dossier concerns an abridged application pursuant to article 10 of Directive 2001/83/EC, as amended, for Dexamethasone sodium phosphate 4 mg/ml and 10 mg/ml solution for injection/infusion referring to the reference medicinal product, "Fortecortin", approved in Europe. Fortecortin 4mg/ml and 10mg/ml solution for injection/infusion were authorised in Germany in 1996 & 1979 respectively.

Together with the indications as approved in Germany for the reference medicinal product Fortecortin, the applicant seeks a new therapeutic indication for the use of Dexamethasone sodium phosphate 4mg/ml and 10mg/ml that is not included in the reference medicinal product, Fortecortin. The additional proposed indication is for the:

- *treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation)*

The applicant has not conducted any clinical studies to support the new indication but rather has submitted the results of a literature review to replace non-clinical and clinical safety and efficacy studies.

Non COVID-19 indications

No clinical studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases.

It is agreed that a bioequivalence study is not required for this application. The product is an aqueous IV solution containing the same active substance in the same concentration as the currently approved product. Although the excipients in the test and reference formulations differ slightly, these differences will not affect the disposition of the drug substance. Please see the PK section of this assessment report.

The clinical overview refers to 46 publications up to year 2020.

The applicant's clinical efficacy section in the clinical overview consists of 4 sections. In the efficacy section the applicant discussed studies which investigated the efficacy of dexamethasone in the following conditions: multiple myeloma, acute lymphocytic leukaemia, patients recovering from surgery, in cardiac surgery and inflammatory neuropathy. In addition, some publications were provided regarding the use of chemotherapy-induced nausea and vomiting, patients with brain tumours or for the treatment in preterm infants.

In relation to **non COVID-19** indications it is considered that the provided clinical overview is inadequate as no discussion was provided for many indications for which the approval is being requested. The applicant is requested to amend the efficacy section of the clinical overview with adequate literature support for all proposed indications. The proposed posology also needs to be discussed **(OC).**

In addition, the applicant provided the English translation of the SmPC of the reference product (i.e Fortecortin Inject). It is noted that the proposed indications and posology included in the SmPC of the reference product differ from those included in section 4.1 and 4.2 of the SmPC for Dexamethasone Taw. Some of these differences could be considered as significant; others are mostly related to changes in the wording.

For example, it is noted that Fortecortin 10mg/ml formulations are only approved for the following indications: brain oedema triggered by brain neoplasm, polytraumatic shock/prophylaxis for post-traumatic acute respiratory distress syndrome and anaphylactic shock (after an epinephrine injection first). The remaining indications especially those related to local administration and ophthalmology are applicable for lower concentration formulations (4 mg/mL) only. This is not reflected for the proposed indications for Dexamethasone Taw **(part MO).**

Further, some differences in posology as compared to the SmPC of the innovator product were noted for two indications i.e prophylaxis and treatment of cytostatic-induced vomiting in anti-emetic regimens and prophylaxis and treatment of post-operative vomiting. The applicant is requested to comment on and justify these differences. An adequate literature support should be provided **(part MO).** For other non-Covid -19 indications, the posology was in line with the innovator product.

COVID-19 indication

The applicant seeks a new therapeutic indication for the use of Dexamethasone sodium phosphate Taw 4mg/ml and 10mg/ml in COVID-19 that is not included in the reference medicinal product, Fortecortin.

The proposed indication for COVID-19 is:

- treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation).

The main supportive study for this indication is the RECOVERY trial. Additional publications in relation to the treatment of COVID-19 patients were also provided.

Of the 11,303 patients who underwent randomization from March 19 to June 8, 2020, a total of 9355 patients (83%) were eligible to receive dexamethasone (i.e., the drug was available in the hospital at the time and the patient had no known indication for or contraindication to dexamethasone). Of these patients, 6425 underwent randomization to receive either dexamethasone (2104 patients) or usual care

alone (4321 patients). The remaining patients were randomly assigned to one of the other treatment groups being evaluated in the trial.

The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and, among patients not receiving invasive mechanical ventilation at the time of randomization, subsequent receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Other prespecified clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation.

Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002).

Allocation to dexamethasone was associated with a shorter duration of hospitalisation than usual standard of care ("no additional treatment" arm) (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.11 [95% CI 1.04 to 1.19]; p=0.002) with the greatest effect seen among patients receiving invasive mechanical ventilation at baseline (test for trend p=0.002).

Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower among those allocated to dexamethasone (risk ratio 0.91 [95% 0.82 to 1.00]; p=0.049), but with significantly greater effects among patients receiving oxygen at randomisation (test for trend p=0.008).

The risk of progression to invasive mechanical ventilation was lower among patients allocated to dexamethasone group vs. usual standard of care group (risk ratio 0.76 [95% CI 0.61 to 0.96]; p=0.021).

The greatest benefit of dexamethasone was found in patients under 70 years of age (for both the oxygen only and mechanical ventilation groups). No evidence of dexamethasone efficacy was demonstrated in patients who were not receiving respiratory support at randomisation.

Based on the review of available data, EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 mg once a day for up to 10 days.

The following indication and posology was agreed for the COVID-19 indication:

Section 4.1 – Therapeutic indications

<invented name> is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy. […]

Section 4.2 – Posology and methods of Administration […]

For the treatment of Covid-19 Adult patients 6 mg IV or PO, once a day for up to 10 days. Paediatric population Paediatric patients (adolescents aged 12 years and older) are recommended to take 6 mg/dose IV or PO once a day for up to 10 days. Duration of treatment should be guided by clinical response and individual patient requirements. Elderly, renal impairment, hepatic impairment - No dose adjustment is needed.

The applicant is requested to update the indication **(MO)** and other sections of the SmPC (i.e 4.2, 4.4 and 5.1) as well as the package leaflet in line with the outcome of the Article 5(3) referral procedure **(OC).**

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances

Not applicable.

2.2.14. Conclusions on clinical efficacy

Major objections were identified in relation to efficacy. The proposed indications are not agreed. In relation to the non COVID-19 indications, some differences as compared to the innovator product were noted and adequate literature support for these differences was not provided.

2.2.15. Clinical safety

In this Article 10(3) application, the applicant has stated that the drug product Dexamethasone Taw contains the same qualitative and quantitative composition in active substance and similar excipients as the German reference product, Fortecortin Inject. However, Dexamethasone Taw contains 2 additional excipients, which are not contained in the reference product, namely methylparaben and propylparaben. These excipients may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Dexamethasone is a well-known medicinal product with recognised efficacy and an established safety profile. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU. However, the use of dexamethasone in patients with COVID-19 is still under investigation.

No new clinical studies on the proposed medicinal product have been conducted. Instead, literature data are submitted in support of this MAA as an abridged medicinal product. The applicant has stated that their overview of safety presented in the clinical overview, section 2.5.5 is based on published information on dexamethasone revealed by data research in MEDLINE and EMBASE databases.

Together with the indications as approved in Germany for the reference medicinal product Fortecortin Inject, the applicant seeks a new therapeutic indication for the use of Dexamethasone sodium phosphate Taw 4mg/ml and 10mg/ml that is not included in the reference medicinal product, Fortecortin Inject. The additional proposed indication is for the:

- *treatment of hospitalised adult patients with COVID19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation)*

To support the proposed indication for the treatment of COVID-19, the applicant submitted a preliminary report which was published on 17 July 2020 in the New England Journal of Medicine (NEJM) concerning the dexamethasone arm of the RECOVERY trial. No safety data from the Recovery trial was provided in the published NEJM paper.

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY, www.recoverytrial.net) is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

The trial was conducted at 176 National Health Service (NHS) hospital organizations in the United Kingdom. Around 15% of all UK hospitalised patients with COVID-19 were enrolled in the trial.

In their submission the applicant included 47 references from the literature, including he National Institutes of Health COVID-19 Treatment Guidelines [Internet]. 2020 (cited 2020 June 29), University of Liverpool COVID-19 Drug Interactions, the Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance and the SmPC of an already approved dexamethasone product.

Patient exposure

The applicant has not provided specific information in the clinical overview regarding patient exposure.

To date, the RECOVERY ((Randomised Evaluation of COVid-19 thERapY) trial is the main interventional clinical trial investigating the effectiveness of dexamethasone in hospitalised patients.

One of the arms in the RECOVERY trial was to study the effect of dexamethasone in hospitalised adult patients with COVID-19. 2104 patients were randomised to receive dexamethasone versus 4321 who received usual care. Treatment with dexamethasone was either 6mg daily orally or 6mg intravenously for up to 10 days, or until discharge, if sooner. It is noted that the strengths of Dexamethasone Taw included in this application are:

Dexamethasone Taw 4 mg/ml solution for injection/infusion

Dexamethasone Taw 10 mg/ml solution for injection/infusion

There is no 6mg/ml solution for injection/infusion presentation for Dexamethasone Taw.

Initially, recruitment was limited to patients aged at least 18 years but this age limit was removed from 9 May 2020. Pregnant or breast-feeding women were eligible. 36% of the patients in the dexamethasone arm of the trial were female and the mean age of the participating patients was 66.1 years.

On 22 June 2020, preliminary results of this clinical study, investigating the effect of dexamethasone in hospitalised adult patients with COVID-19, were reported. A preliminary report was published on 17 July 2020 in the New England Journal of Medicine (NEJM). No safety data from the Recovery trial was provided in the published NEJM paper.

In this recent publication, the results for the comparison of dexamethasone 6 mg (either orally or intravenously) once daily for up to ten days versus usual standard of care alone were reported. It is not known from the trial what percentage of the patients received oral versus iv dexamethasone.

The primary outcome was 28-day mortality. The results of this study indicated a potential benefit of dexamethasone in adult hospitalised patients with COVID-19 receiving invasive mechanical ventilation or oxygen supplementation.

The outcome of a review of the results of the RECOVERY trial, to provide an opinion on the use of dexamethasone medicines for the treatment of COVID-19, was published on the EMA website on 18th September 2020. This review of the dexamethasone arm of the RECOVERY trial was initiated in July 2020 at the request of the EMA Executive Director under Article 5(3) of Regulation 726/2004 following preliminary discussion with the COVID-19 EMA pandemic task force (COVID-ETF). The COVID-ETF brings together experts from across the European medicines regulatory network to provide advice on the development, authorisation and safety monitoring of medicines and vaccines for COVID-19. The review was carried out by EMA's Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use. The CHMP completed its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital. The CHMP has concluded that dexamethasone can be considered to be a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation).

Adverse events

The applicant has referenced a study by San Miguel et al, 2013 comparing the efficacy of one combination therapy (pomalidomide) with high doses of dexamethasone for the treatment of refractory/relapsed and refractory myeloma, not responding to more conventional treatments. 302 patients were randomly assigned to receive pomalidomide plus low dose dexamethasone and 153 to receive high dose dexamethasone. The most common haematological adverse events in both arms were neutropenia, anaemia and thrombocytopenia. The most common non-haematological adverse events were pneumonia, bone pain and fatigue. The results showed that 5% of the patients in high-dose dexamethasone group suffered treatment-related adverse events, some of them with fatal outcome.

The applicant refers to a publication by Nahaczewski, Fowler e Harihan, 2004 in the Journal of Neuroscience Nurs, 2004 entitled "Dexamethasone therapy in patients with brain tumours – a focus on tapering". The paper states the following: "the myriad of adverse effects from corticosteroid therapy is well known to physicians, nurses, pharmacists and patients. Commonly encountered adverse effects include hyperglycaemia, gastritis, gastrointestinal bleeding, weight gain, moon face, osteoporosis with chronic therapy, psychosis or euphoria, immunosuppression causing increased susceptibility to infection, skin fragility and striae (DeAngelis 1994; Vecht et al, 1994)". This paper states that, in general, adverse effects are associated with chronic corticosteroid therapy, although some patients my experience adverse effects on short-term therapy. It also discusses the fact that dexamethasone may cause suppression of the HPA axis and that frequent measurements of blood pressure, weight, height, intraocular pressure and clinical evaluation may be initiated to avoid some of the more common effects, such as the presence of infection, psychological disturbances, thromboembolism, peptic ulcers, cataract and osteoporosis.

The FDA prescribing information, side effects and uses of dexamethasone on drugs.com, is also referenced by the applicant in this section. The applicant has also presented sections 4.8 and 4.9 of the SmPC for dexamethasone Kern Pharma, an already authorised product**.**

Common (≥ 1/100 and ≤ 1/10)

Immune system disorders: reduction in resistance to infection, oropharyngeal candidiasis

Endocrine disorders: hyperglycaemia, adrenocortical insufficiency. At high doses: signs of adrenal hyperactivity (Cushing's syndrome) with acneiform eruptions

Metabolism and nutrition disorders: polyphagia

Eye disorders: cataracts

Vascular disorders: at high doses: hot flashes

Gastrointestinal disorders: at high doses: gastric ulcer

Skin and subcutaneous tissue disorders: delayed wound healing, local allergic reaction. At high doses: hirsutism, cutaneous hyperpigmentation, scleroderma

Musculoskeletal and connective tissue disorders: with prolonged treatments: osteoporosis, bone fragility and muscular atrophy.

Uncommon (≥1/1000 and ≤1/100 of patients):

Blood and lymphatic system disorders: Lymphopenia, eosinopenia.

Immune system disorders: generalised allergic reaction.

Endocrine disorders: amenorrhea.

Metabolism and nutrition disorders: hypopotassemia, acute pancreatitis.

Nervous system disorders: intracranial hypertension, neurological alterations, psychotic states.

Cardiac disorders: heart failure.

Vascular disorders: thromboembolism, oedema, hypertension

Skin and subcutaneous tissue disorders: perspiration.

Musculoskeletal and connective tissue disorders: myopathy

General disorders and alterations at the site of administration: With the rapid intravenous administration of high doses: allergic reactions and infection at the local injection site, generalized anaphylaxis, flare on face or cheek, irregular heart-beats or palpitations, convulsive crises.

Not known (frequency cannot be estimated from the available data):

General disorders: hiccup.

Some adverse reactions, mainly occurring during long-term use, require medical care, such as: acne or other skin problems, avascular necrosis, Cushing's syndrome, oedema, endocrinological disequilibrium, gastrointestinal irritation, hypopotassemia syndrome, osteoporosis or bone fractures, pancreatitis, peptic ulcer or intestinal perforation, scarring at the injection site, steroid myopathy, striae, tendon rupture unusual bruising, and haematoma, wounds that do not heal.

Assessor's Review of Clinical Study Reports submitted by the applicant, for adverse events and safety data.

Table 5: Review of clinical studies which investigated use of dexamethasone in treatment of COVID-19 or ARDS (not caused by COVID-19)

#	Title	Authors	Study Type	Safety Data
1	Effect of Dexamethasone in Hospitalized Patients with COVID-19 Preliminary Report	RECOVERY Collaborative Group, 2020	Randomized, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual care in patients hospitalized with COVID-19.	Results (Subsidiary clinical outcomes) • Preliminary analyses indicate no excess risk of any particular cause of death (in particular there was no excess of deaths due to non-COVID infection). • More detailed analyses of cause-specific mortality, need for renal dialysis or hemofiltration, and duration of ventilation are in preparation.
2	Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective	Singh A. K. et al, 2020	Systematic review on the role of corticosteroid in the management of patients with COVID-19.	3.2. 'Studies with corticosteroid treatment in previous corona virus infections' • One meta-analysis showed a considerable higher mortality (Risk ratio [RR] 1.75; 95% confidence interval [CI], 1.30e2.36; p ¼ 0.0002) and higher rate of secondary infection (RR 1.98; 95% CI, 1.04e3.78; p ¼ 0.04) in steroid treated influenza patients [18]. Methylprednisolone was used in a significant number of studies followed by hydrocortisone, prednisolone and dexamethasone. Section 3.3.2 'Studies where corticosteroid was used to evaluate its outcome' • Of the 5 studies (4 retrospective and 1 quasi-prospective study) conducted with corticosteroids, 3 studies have shown a benefit, while 2 studies shown no benefit, and there was a suggestion of significant harm especially in the critical cases in one sub-study (propensity-matched adjusted hazard ratio [HR] 2.90; 95% CI, 1.17e7.16; p ¼ 0.021) [28-32]. Discussion

				• Corticosteroid use in previous viral respiratory illnesses have also demonstrated a delayed viral clearance [9,10,17]. Similar results have been shown in convalescent COVID-19 patients as well [26].
3	Short-Term Dexamethasone in Sars-CoV-2 Patients	SELVARAJ V. et al, 2020	Case Series (21 patients with SARS-CoV-2 and treated with a short course of dexamethasone, alone or in addition to current investigative therapies).	Patients excluded from this study: • Patients with associated COPD exacerbation who were primarily managed with systemic steroids. • Patients with Diabetic ketoacidosis, hyperglycemic hyperosmolar state, active concurrent bacterial infections. • Patients with a history of steroid-induced mania or psychosis. Results: Dexamethasone was discontinued early in one patient due to hyperglycemia.
4	Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial	Villar J., et al, 2020	Multicentre, randomised controlled trial in a network of 17 intensive care units (ICUs) in Spain (Between March 28, 2013, and Dec 31, 2018).	This trial was stopped by the data safety monitoring board due to low enrolment rate after enrolling more than 88% (277/314) of the planned sample size in December 2018. Findings • The proportion of adverse events did not differ significantly between the dexamethasone group and control group. • The most common adverse events were hyperglycaemia in the ICU (105 [76%] patients in the dexamethasone group vs 97 [70%] patients in the control group), new infections in the ICU (eg, pneumonia or sepsis; 33 [24%] vs 35 [25%]), and barotrauma (14 [10%] vs 10 [7%]). Results • Within the 28-day period after randomisation, 19 patients (12 [8·6%] in the dexamethasone group vs seven [5·1%] in the control group)

				developed extubation failure and were reintubated or reconnected to mechanical ventilation. • The prevalence of pneumothorax was similarly distributed in both groups (14 [10%] of 139 patients in the dexamethasone groups vs ten [7·3%] of 138 patients in the control group; p=0·41; appendix p 16).
5	The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis	Yang Z., et al, 2020	Systematic literature review and meta-analysis.	Results (based on 2 studies included in the meta-analysis which collected adverse reactions data) • Patients treated with corticosteroids were more likely to have adverse reactions such as bacterial infection (RR = 2.08, 95%CI = 1.54–2.81, P < 0.001, I 2 = 0.0%, P = 0.926) and hypokalemia (RR = 2.21, 95%CI = 1.07–4.55, P = 0.032, I 2 = 53.1%, P = 0.104). • However, there was no relationship between corticosteroid therapy and the development of hyperglycemia (RR = 1.37, 95%CI = 0.68–2.76, P = 0.376, I 2 = 74.2%, P = 0.049) or hypocalcemian (RR = 1.35, 95%CI = 0.77–2.37, P = 0.302, I 2 = 80.4%, P = 0.024).
6	Coronavirus Disease 2019 (COVID-19) Treatment Guidelines	NIH, 2020	Treatment guidelines	Additional Considerations • Safety and efficacy of co-administering remdesivir and dexamethasone are not known. • Safety and efficacy of using dexamethasone in these patients are unknown. • Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections).

Table 6: Review of clinical studies which investigated use of dexamethasone in treatment of other conditions

#	Title	Authors	Study Type	Safety Data
1	Safety and efficacy of aprepitant, ramosetron, and dexamethasone for chemotherapy-induced nausea and vomiting in patients with ovarian cancer treated with paclitaxel/carboplatin	Choi C. H., 2014	Prospective non-randomized single site study. Patients received day 1, 125 mg aprepitant, 0.6 mg ramosetron, and 20 mg dexamethasone before chemotherapy; and days 2– 3, 80 mg aprepitant each day.	Results (Tolerability) • Among 460 cycles, adverse events, drug-related adverse events, and serious adverse events occurred in 179 (38.9 %), 35 (7.6 %), and 10 cycles (2.2 %). • The most common adverse events, regardless of cause, were constipation (12.4 %) and headache (11.1 %). • There were four cases of infection and two cases of neutropenic fever. • Of the grade 3 or 4 hematologic toxicities, there were 18 cycles (3.9 %)]of neutropenia and 6 cycles (1.3 %) of thrombocytopenia.
2	Intraoperative High-Dose Dexamethasone for Cardiac Surgery	Dieleman et al, 2012	Randomised controlled trial. Patients were randomly assigned to receive a single intraoperative dose of 1 mg/kg dexamethasone (n=2239) or placebo (n=2255).	• No statistically significant benefit of intraoperative dexamethasone on incidence of the primary study end point of major adverse events (P = .07). • Dexamethasone was associated with reductions in postoperative infection, duration of postoperative mechanical ventilation, and lengths of intensive care unit and hospital stays. • In contrast, dexamethasone was associated with higher postoperative glucose levels.

Table 7: References that did not add to safety or adverse event data

#	Title	Authors	Study Type	Comments
1	Preemptive analgesia of dexamethasone as compared to ketorolac tromethamine in simple tooth extractions*	Menezes C., et al, 2014	Double-blind, crossover and randomized trial with 51 patients	• No safety data was collected.
2	Dose ranging study on the effect of preoperative dexamethasone on postoperative quality of recovery and opioid consumption after ambulatory gynaecological surgery	De Oliveira G. S. J., et al, 2011	Prospective, double-blind trial of 106 females undergoing outpatient gynaecological laparoscopy.	• Study did not evaluate potential side-effects of dexamethasone such as hyperglycaemia, wound healing, and susceptibility to infection. • However, examination of the charts of the subjects at the follow up visit with the surgeon revealed no reports of problems with wound healing or infection.

Serious adverse events and deaths

The applicant has not conducted any new clinical studies in support of this application. To support the additional proposed indication for dexamethasone Taw in addition to the indications already authorised for the reference product, the applicant has submitted the preliminary results of the RECOVERY trial.

In the RECOVERY trial it was stated that suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation. However, no safety data was provided or published in the NEJM. In the outcome of the Article 5(3) referral published on the EMA website, it was stated that '*There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved'.* There were no deaths associated with these SAEs. All of these adverse reactions are expected with dexamethasone.

Laboratory findings

No data provided.

Safety in special populations

Use in children

Regarding the use of dexamethasone in children, the applicant refers to the FDA prescribing information, side effects and uses of dexamethasone on drugs.com. The applicant has also referenced a number of publications, namely Stark et al, 2001, Onland et al, 2009, Sarocco et al, 2005, Papile LA et al, 1998 and Bhuta e Ohlsson, 1998.

The Stark et al, 2001 paper is investigating the adverse effects of early dexamethasone treatment in extremely low-birth weight infants. 220 infants with a birth weight of 501 to 1000 g who were treated with mechanical ventilation within 12 hours after birth were randomly assigned to receive dexamethasone or placebo with either routine ventilatory support or permissive hypercapnia. The dexamethasone was administered within 24 hours after birth at a dose of 0.15 mg per kilogram of body weight per day for three days, followed by a tapering of the dose over a period of seven days. The primary outcome was death or chronic lung disease at 36 weeks postmenstrual age.

During the first 14 days, spontaneous gastrointestinal perforation occurred in a larger proportion of infants in the dexamethasone group (13 percent, vs. 4 percent in the placebo group; P=0.02). The dexamethasone-treated infants had a lower weight (P=0.02) and a smaller head circumference (P=0.04) at 36 weeks' postmenstrual age. The authors of the study conclude that the use of dexamethasone in low-birth weight infants is of limited benefit, and associated with gastrointestinal perforation and growth problems.

Onland et al, 2009 paper is in relation to "Finding the Optimal Postnatal Dexamethasone Regimen for Preterm Infants at Risk of Bronchopulmonary Dysplasia: A Systematic Review of Placebo-Controlled Trials". The authors conclude that a larger randomised study is required.

Sarocco et al, 2005 investigates Steroid Withdrawal Syndrome During Steroid Tapering in Childhood Acute Lymphoblastic Leukemia - A Controlled Study Comparing Prednisone Versus Dexamethasone in Induction Phase. The authors conclude that further prospective studies are required.

Papile LA et al, 1998 concerns a multicentre trial of 2 dexamethasone regimens in ventilator-dependent premature infants. Dexamethasone was associated with an increased incidence of nosocomial bacteremia (relative risk, 1.5; 95 percent confidence interval, 1.1 to 2.1) and

hyperglycemia (relative risk, 1.9; 95 percent confidence interval, 1.2 to 3.0) in the dexamethasone–placebo group, elevated blood pressure (relative risk, 2.9; 95 percent confidence interval, 1.2 to 6.9) in the placebo–dexamethasone group, and diminished weight gain and head growth (P<0.001) in both groups.

Bhuta e Ohlsson, 1998 is a systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease. The authors concluded that dexamethasone treatment within the first 14 days after birth can prevent chronic lung disease (CLD) without clinically significant side effects, but recommend caution because of lack of data concerning long-term neurodevelopmental outcomes.

Section 4.2 of the currently authorised SmPC for the reference product Fortecortin and for the proposed SmPC for Dexamethasone Taw provides posology for the treatment of children (no particular paediatric age groups specified) for the following indications:

- Cerebral oedema due to bacterial meningitis
- Post-traumatic shock/prophylaxis for post-traumatic acute respiratory distress syndrome
- Anaphylactic shock
- Severe acute asthmatic attack
- Prophylaxis and treatment of post-operative vomiting

In section 4.4 of the currently authorised SmPC for the reference product Fortecortin and for the proposed SmPC for Dexamethasone Taw, there is a warning regarding the use of dexamethasone in children and adolescents, in the currently approved indications, as outlined below.

Children and adolescents

"Preterm neonates

Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours after birth) of premature infants with chronic lung disease at starting doses of 0.25 mg/kg twice daily.

In the growth phase of children, the benefit-risk balance of treatment with dexamethasone should be carefully weighed".

The applicant's proposed indication for the treatment of COVID-19 for Dexamethasone Taw is for the treatment of adults only. It is unclear how many children and adolescents were included in the dexamethasone arm of the RECOVERY trial. Initially, recruitment to the trial was limited to patients aged at least 18 years but this age limit was removed from 9 May 2020.

Use in the elderly

In relation to the use of dexamethasone in the elderly population, section 4.4 of the reference product Fortecortin and of the proposed SmPC for Dexamethasone Taw states:

"Because elderly patients are at an increased risk of osteoporosis, the benefit-risk balance of treatment with Fortecortin Inject should be carefully weighed".

There were no safety data provided in the NEJM publication in relation to the dexamethasone arm of the RECOVERY trial. Therefore, the safety profile in relation to the elderly population for the use of dexamethasone to treat COVID-19 is not known. It is noted that this cohort of patients is likely to have other co-existing conditions present, such as cardiovascular, renal or respiratory disease. In the

RECOVERY trial, 54% (1141) of the patients recruited were under 70 years of age, 22% (469) were aged 70 to 79 and 23% (494) were 80 years of age or older.

There are limited safety data in relation to the use of dexamethasone for the treatment of COVID-19 in elderly patients, in particular in over 70 year olds and those with co-existing disease. There is limited information on patients older than 80 years, especially in ventilated patients. In addition, the effects of dexamethasone with oxygen or mechanical ventilation were lower in those with co-existing illness such heart disease chronic underlying lung disease, compared to patients without prior underlying disease.

Use in pregnancy, Fertility and lactation

Section 4.6 of the SmPC of the reference product and of the proposed SmPC for Dexamethasone Taw states the following in relation to use in pregnancy and breast-feeding:

Pregnancy

Dexamethasone crosses the placenta. During pregnancy, especially in the first trimester, this medicine should only be administered after careful benefit-risk assessment.

In long-term treatment with glucocorticoids during pregnancy, foetal growth disorders cannot be excluded.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, including cleft palate, intra-uterine growth retardation and effects on brain growth and development.

There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in humans (see section 5.3).

If glucocorticoids are administered towards the end of pregnancy, there is a risk of atrophy of the foetal adrenal cortex, which may necessitate replacement therapy in the newborn, which has to be slowly reduced.

Breast-feeding

Dexamethasone is excreted in breast milk. There have been no known cases of harm to the infant.

Nevertheless, the medicine should be used under strict indications during lactation. If the disease requires higher doses, breast-feeding should be discontinued.

Furthermore section 5.3 of the reference medicinal product contains the following information:

Acute toxicity:

In mice and rats, the LD50 for dexamethasone after a single oral dose is 16 g/kg body and over 3 g/kg body weight, respectively, within the first 7 days. Following a single subcutaneous dose, the LD50 in mice is more than 700 mg/kg body weight and in rats about 120 mg/kg body weight, within the first 7 days. Over a period of 21 days, these values become lower, which is interpreted as a consequence of serious infectious diseases caused by the hormone-induced immunosuppression.

Chronic toxicity:

There are no data on chronic toxicity in humans and animals. Corticoid-induced intoxications are not known. In longer-term treatment with doses above 1.5 mg/day, pronounced undesirable effects can be expected (see section 4.8).

Mutagenic and tumorigenic potential:

The available study findings for glucocorticoids show no evidence of clinically relevant genotoxic properties.

Reproductive toxicity:

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure.

Moreover, intrauterine growth can be delayed. All these effects were seen at high dosages.

Use in patients with renal impairment

There are no instructions for the use of dexamethasone in patients with renal impairment included in the SmPC of the reference product Fortecortin or the proposed SmPC for Dexamethsone Taw.

However, a warning has been included in section 4.4 of both SmPCs stating that:

At high doses, sufficient potassium intake and sodium restriction should be ensured and serum potassium levels should be monitored.

In addition, section 5.2 of the product information states that:

Renal dysfunction does not substantially affect the elimination of dexamethasone.

Others

In this section, the applicant refers to a number of publications which outline warnings associated with the use of dexamethasone. These are drugs.com, the US National Library for Medicine 2014, van leeuwen, the NIH COVID-19 guidelines, 25th June 2020 and the Massachusetts General Hospital (MGH) COVID-19 treatment guidance. The warnings referred to include the use of dexamethasone in patients with thyroid disorders, liver cirrhosis and diabetes mellitus. The association of dexamethasone with cataract is highlighted by the applicant. In addition, the use of vaccinations and the increased susceptibility of patients to infection, associated with the use of dexamethasone, are also highlighted by the applicant.

Information in relation to these warnings are included in the SmPC of both the reference product Fortecortin Inject and Dexamethasone Taw.

In relation to the COVID-19 indication, the applicant refers to the NIH COVID-19 Guidelines, 25th June 2020 and the Massachusetts General Hospital MGH) COVID-19 Treatment Guidance.

The NIH COVID-19 Guidelines were updated in June 2020. The update to the guidelines was based on a preliminary analysis of the data from the RECOVERY trial. Based on this preliminary analysis of the data, the COVID-19 NIH treatment guidelines Panel made the following recommendations:

- using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**
- **against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**

Recommendation Rating Scheme

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomised trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion.*

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

The applicant has discussed/highlighted drug-drug interactions with dexamethasone. The applicant states that Dexamethasone is metabolised in the liver and inhibition of the catalytic activity of CYP3A4 by other drugs or dietary constituents can affect the metabolism and elimination of dexamethasone. In addition, dexamethasone is also a microsomal enzyme inducer. Thus, several drug-drug interactions are expected. The applicant has discussed the possible interaction of dexamethasone with remdesivir, aminoglutethimide, barbiturates/carbamazepine, digitalis, oestrogens, including the contraceptive pill, indomethacin and other ulcerogenic drugs, isoniazid, itraconazole, ketoconazole NSAIDs including aspirin and other salicylates, phenytoin, phenobarbital, rifampicin, vaccines and the possible effect of corticosteroids on skin tests.

All of these drug-drug interactions (and others) are included in section 4.5 of the reference product and the proposed SmPC for Dexamethasone Taw, with the exception of remdesivir and aminoglutethamide. The effect of dexamethasone on vaccines is included in section 4.4 of the SmPCs. The applicant is proposing to add the following text to section 4.5 of the SmPC in relation to remdesivir:

"*Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely (University of Liverpool COVID-19 Drug Interactions). Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after IV administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure. Dexamethasone is unlikely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19".*

The applicant refers to the Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance; and the University of Liverpool COVID-19 Drug Interactions.

The MGH COVID-19 guidance states that:

- No data are available for the combination of dexamethasone and remdesivir at this time.
- Dexamethasone is a moderate CYP3A4 inducer; review of potential drug-drug interactions is recommended before initiation. Co-administration with remdesivir is allowable.

The University of Liverpool COVID-19 Drug interactions reference document provided states that:

No clinically significant interaction expected (GREEN).

Interactions with a "green" classification (i.e. no clinically significant interaction) have been checked and are listed at the end of this report, but summaries are not shown.

Discontinuation due to AES

No safety data was provided by the applicant from the RECOVERY trial.

Post marketing experience

There is no post marketing experience with the use of dexamethasone for the treatment of COVID-19.

The applicant presented a number of case reports describing adverse events associated with the use of dexamethasone.

According to a case-report, a 59-year-old male developed intractable hiccups during monthly therapy with high dose dexamethasone for multiple myeloma. (Cersosimo e Brophy, Hiccups with High Dose Dexamethasone Administration: A case report 1998)

In a case-report a 39-year-old man with persistent severe HIV-1- related thrombocytopenia was admitted to the hospital for epistaxis, bleeding gums, petechiae, and bruising. Treatment with intravenous dexamethasone 40 mg/day for four sequential days every 28 days was instituted. The patient underwent splenectomy due to persistent severe thrombocytopenia and bleeding. Afterwards the platelet count was normalised. Previously high-dose dexamethasone has been proposed as treatment for patients with immune-related thrombocytopenia as an alternative to chronic oral corticosteroids. It is believed to be associated with better effectiveness and fewer adverse effects. This case suggests that IV dexamethasone treatment is ineffective and harmful in immunologically suppressed HIVinfected patients. The use of high-dose dexamethasone may therefore not be justified in patients with severe HIV- related thrombocytopenia. (Marroni e Gresele 2000)

In a case-report of a 52-year-old woman, without prior history of psoriasis, developed widespread sterile pustular eruption on the trunk and extremities after 2 days administration of subcutaneous dexamethasone. (Demitsu, et al. 1996)

In a case-report, two cases of hypertrophic cardiomyopathy were reported in preterm newborns secondary to dexamethasone treatment. Full recovery occurred after discontinuing the steroids. (Miranda-Mallea, et al. 1997)

Powell K et al conducted one retrospective, cohort study of 218 infants of less than 1500 g birth weight, needing O2 and/or mechanical ventilation, who received postnatal dexamethasone. The authors concluded that the risk of cerebral palsy was significantly related to the total cumulative dose of dexamethasone. (Powell, et al. 2006)

Bloom SL et al observed that dexamethasone- treated infants had significantly lower birth weights. The average birth weight of dexamethasone-treated infants was smaller by 12 g at 24- 26 weeks, 63 g at 27-29 weeks, 161 g at 30-32 weeks, and 80 g at 33-34 weeks' gestation. (Bloom, et al. 2001)

2.2.16. Discussion on clinical safety

No new clinical studies on the proposed medicinal product have been conducted. Instead, literature data are submitted in support of this MAA as an abridged medicinal product. The applicant has stated that their overview of safety presented in the clinical overview, section 2.5.5 is based on published information on dexamethasone revealed by data research in MEDLINE and EMBASE databases.

Together with the indications as approved in Germany for the reference medicinal product Fortecortin Inject, the applicant seeks a new therapeutic indication for the use of Dexamethasone sodium phosphate Taw 4mg/ml and 10mg/ml that is not included in the reference medicinal product, Fortecortin Inject. The additional proposed indication is for the:

- *treatment of hospitalised adult patients with COVID19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation)*

In the overview of clinical safety, the applicant has highlighted the adverse events related/expected with the current use of dexamethasone and the reactions due to overdose. The applicant has also discussed the current use of dexamethasone in special populations such as in children, in the elderly, during pregnancy and lactation and drug-drug interactions.

Dexamethasone is a well-known medicinal product with an established safety profile and is in widespread use across the EU for a number of indications.

Important identified and potential risks associated with the use of dexamethasone include hypersensitivity, including anaphylaxis to dexamethasone or any excipients, risk of opportunistic infection, aggravation or masking of signs of infection, impaired immune response to vaccines, reduced glucose tolerance, adrenal suppression (associated with long-term use in children), osteoporosis, especially in patients at risk, gastrointestinal ulcers or bleeding, intestinal perforation, cataract, glaucoma or corneal ulcer, exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency, corticosteroid withdrawal syndrome upon interruption/discontinuation of long term glucocorticoid administration, cardiovascular complications at high risk patients (such as post-infarct myocardial rupture, congestive heart failure) and congenital abnormalities.

The product information for the reference product Fortecortin Inject and for Dexamethasone Taw provides the relevant safety information in relation to the use of dexamethasone in the already approved indications. However, the safety information for use of dexamethasone in the treatment of COVID-10 is limited.

To date, the RECOVERY ((Randomised Evaluation of COVid-19 thERapY) trial is the main interventional clinical trial investigating the effectiveness of dexamethasone in hospitalised patients.

The RECOVERY trial is an investigator-initiated, individually randomised, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual standard of care in adult patients hospitalised with COVID-19.

In the RECOVERY trial it was stated that suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation. However, no safety data were provided or published in the NEJM.

The outcome of a review (Article 5(3) referral of the results of the RECOVERY trial, to provide an opinion on the use of dexamethasone medicines for the treatment of COVID-19, was published on the EMA website on 18th September 2020.

In the outcome of the Article 5(3) referral published on the EMA website, it was stated that '*There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved'.* All of these adverse reactions are expected with dexamethasone.

The CHMP completed its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital. The CHMP has concluded that dexamethasone can be considered to be a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation).

The applicant is requested to update their dossier/product information, in line with the outcome and recommendations of the Article 5(3) Referral. **(OC)**

The applicant is requested to provide a summary of any further safety data available from the dexamethasone arm of the RECOVERY trial and also a summary of any additional safety information from any other more recent available literature data**.** The applicant is asked to also discuss the selection of case reports presented in the post-marketing section of the dossier. **(OC)**

The applicant has stated that in this Article 10(3) application, the drug product Dexamethasone Taw contains the same qualitative and quantitative composition in active substance and similar excipients as the German reference product, Fortecortin Inject. However, Dexamethasone Taw contains 2 additional excipients, which are not contained in the reference product, namely methylparaben and propylparaben. These excipients may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm. In addition, there is an EMA reflection paper, EMA/CHMP/SWP/272921/2012, which addresses methyl and propylparaben, as those are the parabens predominantly used in oral

pharmaceutical formulations. The focus of this EMA document is on possible endocrine-disrupting effects in humans. If these excipients are not removed from the product, this would pose additional safety concerns for patients treated with Dexamethasone Taw. This is of particular concern for some of the indications proposed e.g. severe, acute asthma attack, treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy or ventilation. The applicant is requested to further discuss.

There is limited safety information in relation to the use of dexamethasone for the treatment of COVID-19 in the elderly population and during pregnancy and lactation.

There are limited safety data in relation to the use of dexamethasone for the treatment of COVID-19 in elderly patients, in particular in over 70 year olds and those with co-existing disease. There is limited information on patients older than 80 years, especially in ventilated patients. In addition, the effects of dexamethasone with oxygen or mechanical ventilation were lower in those with co-existing illness such heart disease chronic underlying lung disease, compared to patients without prior underlying disease. This should be reflected in section 5.1 of the SmPC. **(OC)**

The applicant is asked to discuss the risk of prolongation of viral excretion from the body, thromboembolic events, sepsis and hyperglycaemia in patients treated with dexamethasone for COVID-19. **(OC)**

It is noted that there is a proposal to include a contraindication in section 4.3 of the SmPC for Dexamethasone Taw for patients with COVID-19 who do not require supplemental oxygen. This should be removed, **(OC)**

The applicant has discussed the possible interaction of dexamethasone with remdesivir, aminoglutethimide, barbiturates/carbamazepine, digitalis, oestrogens, including the contraceptive pill, indomethacin and other ulcerogenic drugs, isoniazid, itraconazole, ketoconazole NSAIDs including aspirin and other salicylates, phenytoin, phenobarbital, rifampicin, vaccines and the possible effect of corticosteroids on skin tests.

All of these drug-drug interactions (and others) are included in section 4.5 of the reference product and the proposed SmPC for Dexamethasone Taw, with the exception of remdesivir and aminoglutethamide. The effect of dexamethasone on vaccines is included in section 4.4 of the SmPCs. The applicant is proposing to add the drug-drug interaction with remdesivir to section 4.5 of the SmPC.

The applicant is requested to further justify the proposed text for remdesivir and to remove the reference to the University of Liverpool from the current proposed text. **(OC)**

The applicant is requested to include the interaction with aminoglutethamide in section 4.5 of the SmPC for Dexamethasone Taw. **(OC)**

It is noted that there is text missing in section 5.3 in the proposed SmPC for Dexamethasone Taw in relation to acute toxicity, chronic toxicity and mutagenic and tumorigenic potential. Section 5.3 of the SmPC for Dexamethasone Taw should be in line with that of Fortecortin Inject, the reference product. **(OC & SmPC issue).**

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical safety

The indication proposed in this application for the treatment of COVID-19 relates to adult use only.

Additional safety data needed in the context of a conditional MA under exceptional circumstances

The applicant has not applied for an authorisation for a conditional MA, nor for a MA under exceptional circumstances.

2.2.17. Conclusions on clinical safety

Dexamethasone is a well-known medicinal product with an established safety profile and is in widespread use across the EU for a number of indications.

There is limited information regarding safety data in the use of dexamethasone for the treatment of COVID-19, in relation to the use of dexamethasone for the treatment of COVID-19 in the elderly population over the age of 70 and use during pregnancy and lactation.

Dexamethasone Taw contains 2 additional excipients. These excipients, namely methylparaben and propylparaben may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm. If these excipients are not removed from the product, this would pose additional safety concerns for patients treated with Dexamethasone Taw. This is of particular concern for some of the indications proposed e.g. severe, acute asthma attack, treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy or ventilation.

2.3. Risk management plan

Please refer to sections 16.2.4 – 16.2.6 below.

2.3.1. Safety Specification

Summary of safety concerns

The Safety Specification (Part II, SI-SVIII) from RMP version 1.1, dated 04/09/2020, was assessed below.

The applicant has not proposed any information for Part II Modules: SI to SVI and has completed these sections as being not applicable.

Part II: Module SVII, Identified and potential risks and SVII.1, Identification of safety concerns in the initial RMP submission. The applicant has stated that "this is a MAA for a hybrid medicine in which the safety concerns available in the RMP from the public domain have been adopted by the MAA (CMDh spread-sheet dexamethasone Procedure No.HR/H/0139/001-002/DC, dated 19-Dec-2019)". The summary of safety concerns for HR/H/0139/001-002/DC procedure is in table 2 SVII, below.

Table 2 SVII: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

The applicant has completed the remaining sections of SVII and has completed these as not applicable.

Part II: Module SVIII – Summary of the safety concerns

For Dexamethasone Taw, the applicant has proposed the following summary of the safety concerns in table below:

Table 3 SVIII: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

There have been a number of points for clarification raised during the safety evaluation of Dexamethasone Taw, which may have an impact on the overall conclusions in the RMP. These are concerning limited/missing information on the populations studied in the RECOVERY trial and other limitations of the clinical trial development programme in the treatment of COVID-19.

Depending on the applicant's response to the safety points for clarification, further updates to the proposed RMP may be required.

Currently the summary of safety concerns, as per table 3 above, proposed by the applicant is not endorsed by the CHMP.

2.3.2. Discussion on safety specification

The applicant is not proposing any important identified risks, important potential risks or missing information in the proposed summary of safety concerns and RMP for Dexamethasone Taw.

Whilst this may be acceptable for the well-established uses and indications for dexamethasone currently approved, the CHMP does not consider that it is acceptable in the COVID-19 indication. Based on the evaluation of safety, the CHMP recommends that additional topics are further discussed in the context of the RMP. It is acknowledged that further conclusions on the safety evaluation will be made following the evaluation of the responses to the safety OCs at day 120, particularly in relation to the following points: Use in elderly, over 70 year olds and in particular > 80 year olds. There is limited information on patients older than 80 years, especially ventilated patients. In addition, the effects of dexamethasone with oxygen or mechanical ventilation were lower in those with coexisting illness such heart disease chronic underlying lung disease, compared to patients without prior underlying disease. This should be reflected in section 5.1 of the SmPC. **(OC)**

More information is required in terms of use in pregnancy and lactation.

The risk of prolongation of the viral excretion from the body, thromboembolic events, sepsis and hyperglycaemia in patients treated with dexamethasone should be discussed **(OC)**.

2.3.3. Conclusions on the safety specification

The applicant is not proposing any important identified risks, important potential risks nor areas where there is missing information.

Having considered the data in the safety specification, the CHMP considers that the following issues should be addressed in terms of sub-populations where the clinical safety data is limited/missing for the treatment of COVID 19:

- Use in elderly, over 70 year olds and in particular > 80 year olds. There is limited information on patients older than 80 years, especially ventilated patients. In addition, the effects of dexamethasone with oxygen or mechanical ventilation were lower in those with coexisting illness such heart disease chronic underlying lung disease, compared to patients without prior underlying disease. This should be reflected in section 5.1 of the SmPC.
- Use during pregnancy and breast feeding
- Risk of prolongation of the viral excretion from the body, thromboembolic events, sepsis and hyperglycaemia in patients treated with dexamethasone should be discussed

2.3.4. Pharmacovigilance plan

The applicant does not propose additional pharmacovigilance activities and considers routine pharmacovigilance activities as sufficient.

However, the CHMP raised the concern that there are gaps in knowledge for some of sub-populations treated with dexamethasone for COVID 19:

- patients > 70 years old and in particular > 80 year olds (in the RECOVERY trial, 54% (1141) of the patients recruited were under 70 years of age, 22% (469) were aged 70 to 79 and 23% (494) were 80 years of age or older);

- pregnant and lactating women.

Further discussion on these concerns is expected, included applicant's proposals on further collection of data in the patient populations for whom the safety information is scarce and the safety profile may differ from other treated populations. The applicant is asked to discuss if additional pharmacovigilance activities are needed to collect further data in these areas of missing information.

Moreover the following risks are still to be discussed:

- risk of prolongation of the viral excretion from the body, thromboembolic events, sepsis and hyperglycaemia (both in euglycemic and diabetic patients) in patients treated with dexamethasone.

The applicant is also asked to discuss if additional pharmacovigilance activities are needed to characterise such risks in the COVID-19 population.

The PRAC, having considered the data submitted, is of the opinion that there are still several points to discuss before concluding whether routine pharmacovigilance is sufficient to identify and characterise the risks of the product in the COVID-19 population or a pharmacovigilance development plan is needed. Depending on the applicant's response to the safety points for clarification, further updates to the proposed PhV Plan may be required.

2.3.5. Risk minimisation measures

The Applicant states that routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

The sentence "*Not applicable as the routine risk minimisation measures in place for dexamethasone are the same as for the reference medicinal product*." should be reconsidered in light of the conclusion of CHMP on PI amendments and in consideration of the additional sought indication for treatment of COVID-19 infection, not currently part of the authorised indication of the reference MP.

Routine Risk Minimisation Measures

As the RMP is a standalone document and new important concerns have been identified for the submitted product, the table V.1. Routine Risk Minimisation Measures should be compiled for Dexamethasone Taw in line with the requirements in guidance EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2 and making sure that all safety concerns from Part II agreed at CHMP/PRAC level are correctly reflected.

The same considerations also apply for Table V.3 Summary of RMMs.

Additional Risk Minimisation Measures

The Applicant considers that routine risk minimization activities (assessor note: still to be described in Part V.1) are sufficient to manage the safety concerns of the medicinal product. No aRMMs are proposed.

Overall Conclusions on the Risk Minimisation Measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in all the proposed indications. However, this might be further updated based on the clarification requested about clinical safety.

2.3.6. Conclusion on the RMP

This assessment concerns the evaluation of the RMP version 1.1, dated 04/09/2020 under accelerated assessment in the context of COVID-19 pandemic of the initial marketing authorisation hybrid application for Dexamethasone Taw.

The reference medicinal product is Fortecortin Inject (Germany).

The application foresees that the product would be authorised in approved indications of the reference medicinal product and in the new sought following indication: treatment of hospitalized adult patients with COVID19 who are on oxygen therapy, non-invasive or invasive ventilation, or ECMO (Extracorporeal Membrane Oxygenation).

The RMP Part III-VI could be acceptable provided an updated RMP and satisfactory responses to the list of questions (section 3), is submitted.

PRAC Outcome

This application was discussed by the PRAC during their meeting week beginning 28th September 2020. The PRAC discussed the RMP for Dexamethasone Taw in the context of its initial MA evaluation and generally agreed with the assessment from the rapporteur.

For the consideration of the CHMP, the PRAC would suggest not to include breastfeeding as missing information in the safety specification. Considering that the patients who receive Dexamethasone for the treatment of COVID-19 will be hospitalised and under ventilation, it is unlikely that they would be able to breastfeed. Therefore, the PRAC would suggest to amend the missing information to cover pregnancy only. The follow-up questionnaire should be reviewed accordingly to only gather information on pregnancy and not on breastfeeding.

The PRAC also agreed that, while a large randomised study is probably not needed at this point, the applicant should provide more information about the different safety profile of the medicine in the proposed COVID-19 indication. The applicant should provide a discussion on this topic and reconsider if additional pharmacovigilance activities are needed in order to collect further data in areas highlighted by the CHMP.

In regards to risk minimisation, the PRAC agreed that routine RMM are sufficient to minimise the risks of the product at the moment.

2.4. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

However, the summary of pharmacovigilance system states that the QPPV resides in the United Kingdom (UK) and the PSMF is located at the same address as the QPPV in the UK. Therefore, the applicant is requested to consider relocation of the QPPV and PSMF because of the UK withdrawal from the EU **(OC)**.

Periodic Safety Update Reports submission requirements

Pending updated PRAC Rapporteur AR following assessment of the applicant's responses to the LoQ.

3. Significance/Conformity of paediatric studies

Not applicable.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

In December 2019, pneumonia was caused by a new coronavirus spread in Wuhan, China. Unbiased sequencing of samples from patients with pneumonia reveals a previously unknown type of beta-coronavirus which is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). The causative agent was named severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) by Coronavirus Study Group, and the disease it caused was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).

Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU.

4.1.2. Available therapies and unmet medical need

Remdesivir is a 'viral RNA polymerase inhibitor' (a medicine that interferes with the production of viral genetic material, preventing the virus from multiplying) given by infusion (drip) into a vein. Remdesivir has been authorised in the European Union under the invented name Veklury, since 3 July 2020. There are no other therapies approved in the EU for the treatment of COVID-19 infections.

4.1.3. Main clinical studies

No clinical studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases. In relation to COVID-19 infection the main study supporting this indication was the Recovery trial. The Randomised Evaluation of COVID-19 Therapy (RECOVERY Trial) was a large-enrollment clinical trial of possible treatments for people in the United Kingdom admitted to hospital with severe COVID-19

infection. As of 17 June 2020, the trial included six proposed interventions: five repurposed drugs and convalescent plasma.

4.2. Favourable effects

Dexamethasone is a well-known medicinal product with recognised efficacy and an established safety profile. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU.

No clinical studies have been conducted for this application. Instead, data were provided based on published information revealed by a literature search in MEDLINE and EMBASE databases.

It is agreed that a bioequivalence study is not required for this application. The product is an aqueous IV solution containing the same active substance in the same concentration as the currently approved product. Although the excipients in the test and reference formulations differ slightly, these differences will not affect the disposition of the drug substance.

In relation to the treatment of COVID-19 infection, in the RECOVERY trial there was clear benefit on 28 day mortality for dexamethasone use seen in the overall population, in patients receiving mechanical ventilation and patients receiving supplemental oxygen.

Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002).

Allocation to dexamethasone was associated with a shorter duration of hospitalisation than usual standard of care ("no additional treatment" arm) (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.11 [95% CI 1.04 to 1.19]; p=0.002) with the greatest effect seen among patients receiving invasive mechanical ventilation at baseline (test for trend p=0.002).

Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower among those allocated to dexamethasone (risk ratio 0.91 [95% 0.82 to 1.00]; p=0.049), but with significantly greater effects among patients receiving oxygen at randomisation (test for trend p=0.008).

The risk of progression to invasive mechanical ventilation was lower among patients allocated to dexamethasone group vs. usual standard of care group (risk ratio 0.76 [95% CI 0.61 to 0.96]; p=0.021).

Based on the review of available data, EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days.

4.3. Uncertainties and limitations about favourable effects

In relation to the treatment of patients with COVID-19 infections the proposed indication is not agreed as it needs to be updated in line with the outcome of Article 5(3) referral procedure.

The greatest benefit of dexamethasone was found in patients under 70 years of age (for both the oxygen only and mechanical ventilation groups). No evidence of dexamethasone efficacy was demonstrated in patients who were not receiving respiratory support at randomisation.

In relation to non COVID-19 indications some differences as compared to the innovator product were noted and for these differences no adequate literature data support were provided. This is in relation to the indications and posology.

For example, it is noted that Fortecortin 10mg/ml formulations are only approved for the following indications: brain oedema triggered by brain neoplasm, polytraumatic shock/prophylaxis for post-traumatic acute respiratory distress syndrome and anaphylactic shock (after an epinephrine injection first). The remaining indications especially those related to local administration and ophthalmology are applicable for lower concentration formulations (4mg/ml) only. This is not reflected for the proposed indications for Dexamethasone Taw.

Some differences in posology as compared to the SmPC of the innovator product were reported for two indications i.e prophylaxis and treatment of cytostatic-induced vomiting in anti-emetic regimens and Prophylaxis and treatment of post-operative vomiting. Although there is overlap between the posology presented in the innovator SmPC and the SmPC for Dexamethasone Taw, the relevant justification needs to be provided.

4.4. Unfavourable effects

Dexamethasone is a well-known medicinal product with recognised efficacy and an established safety profile. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU. The use of dexamethasone however, in patients with COVID-19 is still under investigation.

Important identified and potential risks associated with the use of dexamethasone include hypersensitivity, including anaphylaxis to dexamethasone or any excipients, risk of opportunistic infection, aggravation or masking of signs of infection, impaired immune response to vaccines, reduced glucose tolerance, adrenal suppression (associated with long-term use in children), osteoporosis, especially in patients at risk, gastrointestinal ulcers or bleeding, intestinal perforation, cataract, glaucoma or corneal ulcer, exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency, corticosteroid withdrawal syndrome upon interruption/discontinuation of long term glucocorticoid administration, cardiovascular complications at high risk patients (such as post-infarct myocardial rupture, congestive heart failure) and congenital abnormalities.

The product information for the reference product Fortecortin Inject and for Dexamethasone Taw provides the relevant safety information in relation to the use of dexamethasone in the already approved indications. However, the safety information for use of dexamethasone in the treatment of COVID-10 is limited.

The applicant has not conducted any new clinical studies in support of this application. To support the additional proposed indication for dexamethasone Taw in addition to the indications already authorised for the reference product, the applicant has submitted the preliminary results of the RECOVERY trial.

In the RECOVERY trial it was stated that suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation, however no safety data was provided or published in the NEJM. In the outcome of the Article 5(3) referral published on the EMA website, it was stated that '*There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved'.* There were no deaths associated with these SAEs. All of these adverse reactions are expected with dexamethasone. Further safety data is needed in terms of the use of dexamethasone for the treatment of COVID-19.

Dexamethasone Taw contains 2 additional excipients. These excipients, namely methylparaben and propylparaben may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm. If these excipients are not removed from the product, this would pose additional safety concerns for patients treated with Dexamethasone Taw. This is of particular concern for some of the indications proposed e.g. severe, acute asthma attack, treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy or ventilation.

4.5. *Uncertainties and limitations about unfavourable effects*

Uncertainties remain following the use of dexamethasone for the treatment of COVID-19. This is in terms of sub-populations where the clinical safety data is limited/missing for the treatment of COVID 19, such as:

- Use in elderly, over 70 year olds and in particular > 80 year olds. There is limited information on patients older than 80 years, especially ventilated patients. In addition, the effects of dexamethasone with oxygen or mechanical ventilation were lower in those with coexisting illness such heart disease chronic underlying lung disease, compared to patients without prior underlying disease. This should be reflected in section 5.1 of the SmPC.
- Use during pregnancy and breast feeding
- Risk of prolongation of the viral excretion from the body, thromboembolic events, sepsis and hyperglycaemia in patients treated with dexamethasone should be discussed

In addition, Dexamethasone Taw contains 2 additional excipients. These excipients, namely methylparaben and propylparaben may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm. If these excipients are not removed from the product, this would pose additional safety concerns for patients treated with Dexamethasone Taw.

4.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
All-cause mortality Within 28 days of randomisation	Primary outcome		Dexamethasone	The usual care	Dexamethasone 22.9% The usual care 25.7% rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001)	RECOVERY Study
Time to discharge from hospital	Secondary outcome		Dexamethasone	The usual care	Dexamethasone 12 days The usual care 13 days rate ratio 1.10 [95% CI 1.03 to 1.17]	RECOVERY Study
Unfavourable Effects						
In the Recovery trial it was stated that suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation, however no safety data was provided or published in the NEJM. The investigators provided this information and stated that there were four serious adverse events reported as being related to study treatment (all were expected with dexamethasone). Two were hyperglycaemia (which required a longer admission for stabilisation); there was one case of steroid-induced psychosis and one participant had an upper gastrointestinal bleed. All events resolved and none of the participants died.						

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

On 11 March, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic.

Globally, approximately 30 million confirmed cases of COVID-19 have been reported. In the European Union only Remdesivir has been authorised for the treatment of COVID-19 infections. There are no other therapies currently approved in the EU for this disease.

In the RECOVERY trial, there was clear benefit on 28 day mortality for dexamethasone use seen in the overall population, in patients receiving mechanical ventilation and patients receiving supplemental oxygen.

Allocation to dexamethasone was associated with a shorter duration of hospitalisation than usual standard of care ("no additional treatment" arm) (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.11 [95% CI 1.04 to 1.19]; p=0.002) with the greatest effect seen among patients receiving invasive mechanical ventilation at baseline (test for trend p=0.002).

In relation to the treatment of patients with COVID-19 infections, the wording for the proposed indication is not agreed as it needs to be updated in line with the outcome of Article 5(3) referral procedure

In relation to non-COVID-19 indications, some differences as compared to the innovator product were noted and for these differences no adequate literature support were provided. This is in relation to the indications and posology.

Dexamethasone is a well-known medicinal product with recognised efficacy and an established safety profile. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU. The use of dexamethasone however, in patients with COVID-19 is still under investigation.

Dexamethasone is a well-known medicinal product with an established safety profile and is in widespread use across the EU for a number of indications.

Important identified and potential risks associated with the use of dexamethasone include hypersensitivity, including anaphylaxis to dexamethasone or any excipients, risk of opportunistic infection, aggravation or masking of signs of infection, impaired immune response to vaccines, reduced glucose tolerance, adrenal suppression (associated with long-term use in children), osteoporosis, especially in patients at risk, gastrointestinal ulcers or bleeding, intestinal perforation, cataract, glaucoma or corneal ulcer, exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency, corticosteroid withdrawal syndrome upon interruption/discontinuation of long term glucocorticoid administration, cardiovascular complications at high risk patients (such as post-infarct myocardial rupture, congestive heart failure) and congenital abnormalities.

Dexamethasone Taw contains 2 additional excipients. These excipients, namely methylparaben and propylparaben may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm. If these excipients are not removed from the product, this would pose additional safety concerns for patients treated with Dexamethasone Taw. This is of particular concern for some of the indications proposed e.g. severe, acute asthma attack, treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy or ventilation.

Uncertainties remain following the use of dexamethasone for the treatment of COVID-19. This is in terms of sub-populations where the clinical safety data is limited/missing for the treatment of COVID 19.

4.7.2. Balance of benefits and risks

Globally, approximately 30 million confirmed cases of COVID-19 have been reported. In the European Union only Remdesivir has been authorised for the treatment of COVID-19 infections. There are no other therapies currently approved in the EU for this disease.

In the RECOVERY trial, there was clear benefit on 28 day mortality for dexamethasone use seen in the overall population, in patients receiving mechanical ventilation and patients receiving supplemental oxygen.

However, the proposed indication for Covid 19 needs to be amended in line with the outcome Article 5(3) referral procedure.

In addition, in relation to non-COVID-19 indications, some differences as compared to the innovator product were noted and for these differences no adequate literature support were provided. This is in relation to the indications and posology.

Major objections are raised in relation to these issues.

Dexamethasone is a well-known medicinal product with recognised efficacy and an established safety profile. Dexamethasone has been used in clinical practice for the treatment of many indications and has been in use for many years, throughout the EU. The use of dexamethasone however, in patients with COVID-19 is still under investigation.

Dexamethasone Taw contains 2 additional excipients. These excipients, namely methylparaben and propylparaben may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm. This is of particular concern for some of the indications proposed e.g. severe, acute asthma attack, treatment of hospitalised adult patients with COVID-19 who are on oxygen therapy or ventilation.

A multidisciplinary quality and safety MO has been raised in relation to the presence of methylparaben and propylparaben in Dexamethasone Taw.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4.8. Conclusions

The overall benefit/risk of Dexamethasone Taw is currently negative.