

# Guidance on the format of the risk management plan (RMP) in the EU – in integrated format

## **EU Risk Management Plan for SOLDESAM s.c. (Dexamethasone Sodium Phosphate)**

### **RMP version to be assessed as part of this application:**

RMP Version number: 0.1

Data lock point for this RMP: 14/07/2023

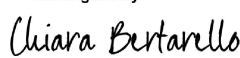
Date of final sign-off: 04/08/2023

Rationale for submitting an updated RMP: *Not applicable as this is initial marketing authorisation application within a line extension procedure*

Summary of significant changes in this RMP: *Not applicable*

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## Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

<b>Active substance(s) (INN or common name)</b>	DEXAMETHASONE SODIUM PHOSPHATE
<b>Pharmacotherapeutic group(s) (ATC Code)</b>	H02AB02 (Systemic hormonal preparations, excluding sex hormones and insulins, corticosteroids for systemic use, glucocorticoids, plain)
<b>Marketing Authorisation Applicant</b>	Laboratorio Farmacologico Milanese S.r.l.
<b>Medicinal products to which this RMP refers</b>	1
<b>Invented name(s) in the European Economic Area (EEA)</b>	SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection
<b>Marketing authorisation procedure</b>	national
<b>Brief description of the product</b>	Chemical class
	Dexamethasone is a synthetic glucocorticoid used principally as an anti-inflammatory or immunosuppressant agent.
	<p>Summary of mode of action</p> <p>Glucocorticoids are produced and secreted by the adrenal cortex and are an integral part of the hypothalamic pituitary adrenal (HPA) axis.</p> <p>Glucocorticoids, both natural (cortisol) and synthetic (as dexamethasone) exert various metabolic effects and modify the body's immune responses to various stimuli.</p> <p>The majority of effects produced by glucocorticoids result from initial steroid binding to intracellular glucocorticoid receptors followed by translocation to the nucleus and changes in gene transcription. In their steroid-free (unbound) state, intracellular glucocorticoid receptors (GR) are bound to stabilizing proteins that include heat-shock protein 90 (Hsp90) and immunophilin. The unbound form of the receptor is not capable of affecting gene transcription. Binding of steroid initiates a conformational change that results in an exchange of chaperone proteins, which permits attachment of the steroid-GR complex to the dynein protein trafficking pathway. This results in translocation of the steroid-GR complex from the cytoplasm into the nucleus. Once in the nucleus, the steroid-GR complex dimerizes and binds to glucocorticoid response elements (GRE) associated with the regulatory region of</p>

	<p>glucocorticoid-sensitive genes. Binding of the glucocorticoid-GR dimer either represses, or stimulates the transcription of sensitive genes, resulting in changes in synthesis of mRNA, followed by changes in protein synthesis. These steps are necessary for producing most cellular responses to glucocorticoids. Both a reduction in the synthesis of inflammatory cytokines, as well as upregulation in the synthesis of annexin A1 are known to play important roles in mediating the anti-inflammatory and immunomodulatory effects of glucocorticoids. In some situations glucocorticoids are able to produce more rapid responses by binding to membrane-associated receptors and exerting effects that do not involve changes in gene regulation.</p> <p>Glucocorticoids are used primarily for their anti-inflammatory effects in multi-organ disorders. Dexamethasone possesses the actions and effects of other basic glucocorticoids and is among the most active compounds of its class.</p> <p>Important information about its composition</p> <p>None</p>
<b>Hyperlink to the Product Information</b>	see annex 4 seq. 0005
<b>Indication(s) in the EEA</b>	<p>Current:</p> <ul style="list-style-type: none"> <li>• Anti-inflammatory corticotherapy <ul style="list-style-type: none"> <li>➤ degenerative and post-traumatic arthrosis, inflammatory arthritis, chronic progressive polyarthritis, ankylosing spondylarthritis;</li> <li>➤ asthma attacks;</li> <li>➤ cerebral oedema, cerebral neoplasms (as an adjuvant);</li> <li>➤ states of emergency and shock: glottis oedema, post-transfusion reactions, anaphylaxis; haemorrhagic, surgical, septic, cardiogenic, burns traumatism.</li> </ul> </li> <li>• Treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (12 years of age and older, weighing at least 40 kg) in case of supplemental oxygen therapy</li> </ul> <p>Proposed (if applicable):</p> <p>Not applicable as this is an initial marketing authorisation applications within a line extension procedure</p>
<b>Dosage in the EEA</b>	<p>Current:</p> <p>The dosage depends on the symptoms severity of the disease, on patient 's individual response of the and, in intra-articular use, on</p>

the size of the joint.

- Intramuscular and intravenous route

- Severe asthma attacks

Adults: 8 - 20 mg i.v.; repeated injections of 8 mg every 4 hours if necessary.

- Brain edema, brain tumors (as adjuvant)

8 mg i.v. followed by 4 mg always i.v. at least every 6 hours.

- States of emergency and shock:

32 - 96 mg i.v., repeated if necessary.

- Coronavirus disease 2019 (COVID19)

Adults: 6 mg i.v., once a day for up to 10 days.

Pediatric population (adolescents over 12 years of age and weighing at least 40 kg): 6 mg i.v., once a day, for up to 10 days.

- Intrasynovial route

Depending on the severity of the disease, no more than 3-4 infiltrations or 3-4 injections per joint should be performed. The interval between injections should not be less than 3-4 weeks.

The infiltrations must take place using the following indicative dosages:

large joints (knee)	2mg	0,5ml
in some case	4mg	1 ml
small joints (temporomandibular joint, interphalangeal joint)	0,8 - 1 mg	0,2 - 0,25 ml
synovial capsules	2 - 4 mg	0,5 - 1 ml
tendon sheaths	0,4 - 1 mg	0,1 - 0,25 ml
soft tissues	2 - 4 mg	0,5 - 1 ml
calluses	0,4 - 1 mg	0,1 - 0,25 ml
tendon cysts	1 - 2 mg	0,25 - 0,5 ml

- Oral route

	<p>Treatment can be started by administering from 2 to 8 mg per day, higher doses may be required in more serious diseases.</p> <p>➤ Treatment of coronavirus disease 2019 (COVID19)</p> <p>Adults: 6 mg/daily for up to 10 days.</p> <p>Pediatric population: 6 mg/ daily for up to 10 days.</p>
	<p>Proposed (if applicable):</p> <p>Not applicable as this is an initial marketing authorisation applications within a line extension procedure.</p>
<b>Pharmaceutical form(s) and strengths</b>	<p>Current (if applicable):</p> <ul style="list-style-type: none"> <li>• 4,37 mg/1 ml, oral solution – solution for injection -3 vials of 1 ml</li> <li>• 4,37 mg/1 ml, oral solution – solution for injection - 3 vials of 2 ml</li> </ul>
	<p>Proposed (if applicable):</p> <p>Not applicable as this is an initial marketing authorisation applications within a line extension procedure</p>
<b>Is/will the product be subject to additional monitoring in the EU?</b>	No

## Part II: Safety specification

### Part II: Module SI - Epidemiology of the indication(s) and target population(s)

**Anti-inflammatory corticotherapy** - degenerative and post-traumatic arthrosis, inflammatory arthritis, chronic progressive polyarthritis, ankylosing spondylarthritis

An estimated 240 million individuals worldwide have symptomatic of osteoarthritis (OA), including 10% of men and 18% of women age 60 and older. Recent estimates from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) found that globally, the age-standardized point prevalence and annual incidence rate of symptomatic, radiographically confirmed hip and knee osteoarthritis were 3754.2 (Uncertainty Index (UI) 3389.4–4187.6) and 181.2 (UI 162.6–202.4) per 100,000, respectively; these represent 9.3% and 8.2% increases since 1990. Of note, GBD utilized available data sources on radiographic osteoarthritis, and when data were not available for a country, values were estimated based on similar countries and territories, using disease-relevant country characteristics. Population-based studies of osteoarthritis prevalence and incidence have been conducted in multiple countries. In a large survey study of individuals age  $\geq 50$  in England, about half of respondents indicated having OA in at least one joint, including the hand, hip, knee and foot[1]. A recent survey study of individuals age  $\geq 20$  years in Spain found that 29% of individuals (weighted prevalence) had OA at one or more locations (including spine, hand, hip and knee), based on screening questions corresponding to American College of Rheumatology (ACR) clinical criteria. A United Kingdom (UK)-based study, using a large nationally representative primary care database, found there were 494,716 incident cases of clinical OA between 1997 and 2017, corresponding to 6.8 (95% Confidence Interval (CI) 6.7–6.9) per 1000 person years (age- and sex-standardized). Another study using this data source showed that among patients age  $\geq 45$  years, the annual age and sex-adjusted incidence rate for clinical OA increased from 29.2 (95% CI 28.8, 29.5) to 40.5 (95% CI 40.3, 40.7) per 1000 person years from 1992 to 2013 [1].

There has also been interest in multiple-joint OA (MJOA), which has been defined in at least 10 different ways. Because of this variability, it has been difficult to establish a consensus of the prevalence of MJOA. A systematic review found prevalence estimates ranging from 5% to 25%. Overall, MJOA has been associated with poorer OA-related outcomes compared with single joint involvement[1].

Risk factors of OA include obesity, female gender, aging, knee injuries, and high-impact sports, such as marathons, speed skating, and weightlifting [2]. Many studies have shown that OA risk increases with age and is greater among women compared with men. Gender differences in OA seem to be present across joint sites, with the potential exception of cervical spine OA. Racial and ethnic differences are also well documented. In the US, multiple studies have found that Blacks have greater prevalence and severity of lower extremity OA than Whites. A recent study of the Osteoarthritis Initiative cohort found that Black participants had lower odds of radiographic (OR = 0.79, 95% CI 0.66, 0.94) and symptomatic (OR = 0.63, 95%CI 0.49, 0.82) hand OA compared to Whites; however, it should be noted that this cohort includes only individuals with or at risk for knee OA. Studies have observed that Chinese women have about 45% higher prevalence of radiographic and symptomatic knee OA than white women, with no difference between Chinese and white men. However, hip OA is less common among Chinese individuals, compared with whites. Studies from multiple countries have shown that OA prevalence, particularly at the knee and hip, is higher among individuals with lower socioeconomic status, as well as in rural communities[1].



There is a clear association of overweight with increased risk for OA, particularly at the knee; one systematic review found that obesity increased the risk of OA about 3-fold[1]. Furthermore, multiple studies have found that higher bone mineral density is associated with greater risk for radiographic knee and hip OA[1]. In addition, also prior traumatic joint injury and subsequent surgery are potent risk factors for OA development [1].

Finally, physically demanding occupations are associated with increased risk for OA. In a recent systematic review, physically demanding occupations including construction workers, floor layers, brick layers, fishermen, farmers, and service personnel were associated with a higher risk for hip and knee OA [1].

The following classes of drugs are currently used to treat OA: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, opioids, chondroprotective agents and anti-cytokines [2].

## **Anti-inflammatory corticotherapy - asthma attacks**

### Incidence and Prevalence:

The World Health Organization estimated that approximately 300 million people currently have asthma worldwide, and with current trends rising, it is expected to reach 400 million by 2025. Annual estimated incidence of physician-diagnosed asthma ranged from 0.6 to 29.5 per 1000 persons. In terms of gender, studies have shown a male predominance in the diagnosis of asthma prior to puberty, but a higher prevalence in females in adulthood, as well as more severe cases of asthma in women than in men. Nearly 250,000 people die prematurely each year from asthma, and most of all these deaths are preventable. Globally, death rates from asthma in children range from 0 to 0.7 per 100,000 people. Among children, asthma is the most common chronic disease, ranking among the top 20 conditions worldwide for disability-adjusted life years in children

Risk factors for incident asthma among children included: male sex, atopic sensitization, parental history of asthma, early-life stressors and infections, obesity, and exposure to indoor allergens, tobacco smoke and outdoor pollutants.

Risk factors for adult-onset asthma included female sex, airway hyperresponsiveness, lifestyle factors, and work-related exposures. Furthermore, there has been increasing interest in the role of vitamin D in asthma. There have been many studies which have suggested that deficiency in vitamin D may play a role in the severity of symptoms[3]. Epidemiologic studies have mostly shown a relationship between early-life exposure to antibiotics and the development of asthma and allergies. In addition to antibiotic exposure, other early-life factors that affect the establishment of the infant microbiome and have been variably associated with the development of asthma and allergies include breastfeeding vs formula feeding and mode of delivery (e.g., caesarean section vs vaginal delivery) [3].

The main existing treatment options are Leukotriene antagonists, Tiotropium, Anti-IL-5, Short-acting  $\beta_2$ -agonists, long-acting  $\beta$ -agonists, Inhaled corticosteroids, Systemic corticosteroids [4].

## **Anti-inflammatory corticotherapy - cerebral oedema, cerebral neoplasms (as an adjuvant)**

Cerebral oedema is a pressing clinical problem. Cerebral oedema and brain swelling inevitably accompany ischemic infarcts and intracerebral haemorrhages and, when severe, may increase mortality to nearly 80%. Even in non-life-threatening stroke, the magnitude of brain swelling is strongly predictive of patients' functional outcome. Cerebral oedema and brain swelling occur in 20–30% of patients with acute liver failure, and increase mortality to 55%.<sup>3</sup> Cerebral oedema and brain swelling after traumatic brain injury are estimated to account for up to 50% of patient mortality [8].

Risk factors include causes of very different nature such as diabetes, ketoacidosis, elevated altitude, brain injury and also neoplasms. The main existing treatment options include hyperosmolar treatments (i.e. mannitol and hypertonic saline solutions), sedation, neuromuscular blockade, hypothermia, and decompressive craniectomy [5].

**Anti-inflammatory corticotherapy** - states of emergency and shock: glottis oedema, post-transfusion reactions, anaphylaxis; haemorrhagic, surgical, septic, cardiogenic, burns, traumas

The main existing treatment options:

The term 'shock' is used to describe a complex, life-threatening clinical condition that arises from acute circulatory failure. Shock is a pathological state that results when the circulation is unable to deliver sufficient oxygen and nutrients to the cells and tissues. The resulting hypoxia, tissue hypoperfusion and cellular dysfunction can lead to multi-organ failure; if this is not treated in a timely and appropriate manner, it can lead to death.

The treatment of cardiogenic shock, septic shock, and hypovolemic shock include the administration of endogenous catecholamines (epinephrine, norepinephrine, and dopamine) as well as various vasopressor agents that have shown efficacy in the treatment of the various types of shock. In addition to the endogenous catecholamines, exogenous catecholamines like Dobutamine, isoproterenol, phenylephrine, and milrinone have served as the mainstays of shock therapy for several decades. Vasopressin, selepressin, calcium-sensitizing agents like levosimendan, cardiac-specific myosin activators like omecamtiv mecarbil (OM), istaroxime, and natriuretic peptides like nesiritide can enhance therapy when shock is especially complex [6].

**Treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (12 years of age and older, weighing at least 40 kg) in case of supplemental oxygen therapy**

Data from the Centres for Disease Control and Prevention collected between February 2020 to September 2021 indicate the following estimated rates of disease outcomes in the US: Infection: 44,650 per 100,000 (44.6%); Symptomatic illness: 37,764 per 100,000 (37.8%); Hospitalisation: 2286 per 100,000 (2.3%); Death: 281 per 100,000 (0.28%).

Older people  $\geq 70$  years of age and males are at increased risk for infection and severe disease. Adolescents appear to have similar susceptibility to infection as adults, and children have a lower susceptibility. However, evidence is conflicting and the detailed relationship between age and susceptibility to infection requires further investigation. Unlike adults, children do not seem to be at higher risk for severe disease based on age or sex. Variants may spread more effectively and rapidly among young children compared with the wild-type virus, although hospitalisation rates decreased.

The incidence of infection in healthcare workers ranged from 0% to 49.6%, and the prevalence of seropositivity ranged from 1.6% to 31.6%. There was no association between age, sex, or healthcare worker role (i.e., nurse versus physician) and the risk for infection, based on moderate-certainty evidence. There was an association between Black race or Hispanic ethnicity and increased risk for infection compared with White race or non-Hispanic ethnicity, based on moderate-certainty evidence. There was an association between use of personal protective equipment and decreased risk for infection, based on moderate-certainty evidence [7].

The main existing treatment options in case of concomitant supplemental oxygen therapy include Antiviral treatment (i.e. remdesivir) and immunomodulatory therapy including corticosteroids.

## Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

### Toxicity

- acute or repeat-dose toxicity studies

LD50 values for dexamethasone sodium phosphate have been found related to various routes of administration:

Species	Route of Exposure or Administration	Dose Data (mg/kg)	Toxic Effects
Mouse	oral	1800	-
Mouse	intraperitoneal	550	-
Mouse	Intravenous	932	-
Rat	Oral	>3000	-
Rat	intraperitoneal	54	Diarrhoea, lacrimation
Rat	subcutaneous	14	-

Repeat-dose toxicity data for dexamethasone:

Route of Exposure or Administration	Species	Dose data	Toxic effects
Oral	Rat	10 mg/kg/5D (intermittent)	Endocrine - changes in spleen weight Nutritional and Gross Metabolic - weight loss or decreased weight gain Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - other Enzymes
Subcutaneous	Rat	5 mg/kg/2W (intermittent)	Cardiac - other changes Vascular - BP elevation not characterized in autonomic section Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - proteases

Intramuscular	Rat	26 mg/kg/13D (intermittent)	Lungs, Thorax, or Respiration - other changes Nutritional and Gross Metabolic - weight loss or decreased weight gainBiochemical - Metabolism (Intermediary) - other proteins
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- reproductive/developmental toxicity

Teratogenic effects are observed following long-term administration of glucocorticoids, although short-term glucocorticoid therapy is still utilized to reduce foetal mortality, respiratory distress syndrome, and intraventricular haemorrhage in preterm infants.

- genotoxicity

Dexamethasone has been observed to be non-mutagenic in the Ames Salmonella/S9 test system. In human lymphocyte cultures, dexamethasone did not cause any significant increase in aberration frequency at any concentration (1.0, 10.0 and 100.0 µg/ml) when the treatment duration was 24 or 48 h. However, at 72 h treatment time, it caused a significant increase ( $p < 0.05$ ) in aberration frequency at 10.0 µg/ml concentration and a more significant increase ( $p$  at 100.0 µg/ml concentration). Delay in cell cycle and reduction in mitotic index were also seen at the higher dose with 72 h treatment duration. This increased clastogenicity by dexamethasone at the longest treatment duration as compared to the shorter treatment durations could be attributable to the inherent ability of the human lymphocytes to metabolize certain compounds per se. Moreover, as dexamethasone has a longer biological half-life (36-54 h) than other corticosteroids, it may require a comparatively longer time to show certain in vitro clastogenicity.

- carcinogenicity

No carcinogenicity studies have been conducted with dexamethasone but in view of the negative results in mutagenicity studies, and the lack of structural similarity with known carcinogens, these are not required.

## **Part II: Module SIII - Clinical trial exposure**

No data on clinical trial patients exposure are available for SOLDESAM s.c. as the MAH did not sponsored and/or performed any clinical trial on this product nor for other products containing dexamethasone from which this line extension was started.

Studies reported in Module 2.5 of the registration dossier of SOLDESAM s.c. come from medical literature only.

## **Part II: Module SIV - Populations not studied in clinical trials**

No data owned by the MAH on clinical trials exposure for SOLDESAM s.c. are available, as the MAH did not sponsored and/or performed any clinical trial neither on this product nor for other products containing dexamethasone from which this line extension was started.

Studies and Trials reported in Module 2.5 of the registration dossier of SOLDESAM s.c. come from medical literature only.

### **SIV.1 Exclusion criteria in pivotal clinical studies within the development programme**

No data owned by the MAH on exclusion criteria in pivotal clinical studies within the development programme for SOLDESAM s.c. are available, as the MAH did not sponsored and/or performed any clinical trial neither on this product nor for other products containing dexamethasone from which this line extension was started.

Studies and Trials reported in Module 2.5 of the registration dossier of SOLDESAM s.c. come from medical literature only.

### **SIV.2 Limitations to detect adverse reactions in clinical trial development programmes**

No data owned by the MAH on limitations to detect adverse reactions in clinical trial development programmes for SOLDESAM s.c. are available, as the MAH did not sponsored and/or performed any clinical trial neither on this product nor for other products containing dexamethasone from which this line extension was started.

Studies and Trials reported in Module 2.5 of the registration dossier of SOLDESAM s.c. come from medical literature only.

### **SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes**

No data owned by the MAH on limitations in respect to populations typically under-represented in clinical trial development programmes for SOLDESAM s.c. are available, as the MAH did not sponsored and/or performed any clinical trial neither on this product nor for other products containing dexamethasone from which this line extension was started.

Studies and Trials reported in Module 2.5 of the registration dossier of SOLDESAM s.c. come from medical literature only.

## **Part II: Module SV - Post-authorisation experience**

This module is not applicable as this RMP applies to an initial marketing authorisation application within a line extension procedure. Therefore, no data on post-authorisation experience on SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection is available.

### **SV.1 Post-authorisation exposure**

#### SV.1.1 Method used to calculate exposure

Not applicable.

#### SV.1.2 Exposure

Not applicable.

## **Part II: Module SVI - Additional EU requirements for the safety specification**

### **Potential for misuse for illegal purposes**

No potential for misuse for illegal purposes as a recreational drug is foreseen by MAH for SOLDESAM s.c.. However, Dexamethasone is an active substance with a potential doping use. It is included in the list "elenco contenente i principi attivi inseriti nelle classi di sostanze vietate per doping" published on the Italian Ministry of Health website. For this reason, according to the Blue Box Requirements (ref. CMDh/258/2012) the appropriate pictogram is reported on the packaging of SOLDESAM s.c..



## Part II: Module SVII - Identified and potential risks

### SVII.1 Identification of safety concerns in the initial RMP submission

#### SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

##### Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Hirsutism

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- De-latency of diabetes mellitus, increased body weight, congestive heart failure, arrhythmias, hypertension, myopathy, osteoporosis; compression fractures of the vertebrae; aseptic necrosis of the femoral and humeral head, premature closure of epiphyses, osteonecrosis, intestinal perforations, pancreatitis, delayed wound healing, thinning of the skin, insomnia, mood and personality swings, suicidal thoughts, severe depression, mania, hallucinations, aggravation of schizophrenia, irritability, convulsions, Cushing's syndrome, adrenal suppression, amenorrhea, increased hepatic enzymes, posterior sub-capsular cataracts; glaucoma, chorioretinopathy, opportunistic infections,

#### SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

**Important Identified Risk 1:** none

**Important Potential Risk:** none

**Missing information 1:** Safety in patients >70 years old and in particular >80 years old (COVID-19 indication)

Risk-benefit impact: no risk-benefit impact has been evaluated by the MAH. This missing information has been included in this RMP according to "Summary of risk management plan for (dexamethasone) for treatment of coronavirus disease 2019 (COVID-19)" published on CMDh web site (ref. CMDh/429/2021).

**Missing information 2:** Safety in pregnant women (COVID-19 indication)

Risk-benefit impact: no risk-benefit impact has been evaluated by the MAH. This missing information has been included in this RMP according to "Summary of risk management plan for (dexamethasone)

for treatment of coronavirus disease 2019 (COVID-19)" published on CMDh web site (ref. CMDh/429/2021).

## **SVII.2 New safety concerns and reclassification with a submission of an updated RMP**

This section is not applicable as this RMP applies to an initial marketing authorisation application within a line extension procedure. Therefore, this is the first RMP submitted for SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection is available.

## **SVII.3 Details of important identified risks, important potential risks, and missing information**

### **SVII.3.1. Presentation of important identified risks and important potential risks**

**Important Identified/Potential Risk:** None.

### **SVII.3.2. Presentation of the missing information**

**Missing information:** Safety in patients >70 years old and in particular >80 years old (COVID-19 indication)

This missing information has been included in this RMP according to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) Minutes for the meeting on 23-24 February 2021 (EMA/CMDh/151813/2021) and to the "Summary of risk management plan for (dexamethasone) for treatment of coronavirus disease 2019 (COVID-19)" published on CMDh web site (ref. CMDh/429/2021).

**Missing information:** Safety in pregnant women (COVID-19 indication)

This missing information has been included in this RMP according to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) Minutes for the meeting on 23-24 February 2021 (EMA/CMDh/151813/2021) and to the "Summary of risk management plan for (dexamethasone) for treatment of coronavirus disease 2019 (COVID-19)" published on CMDh web site (ref. CMDh/429/2021).

## Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	<ul style="list-style-type: none"><li>• Safety in patients &gt;70 years old and in particular &gt;80 years old (COVID-19 indication)</li><li>• Safety in pregnant women (COVID-19 indication)</li></ul>

## **Part III: Pharmacovigilance Plan (including post-authorisation safety studies)**

### **III.1 Routine pharmacovigilance activities**

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

**Specific adverse reaction follow-up questionnaires for safety concern "Safety in patients >70 years old and in particular >80 years old (COVID-19 indication)":** none

**Specific adverse reaction follow-up questionnaires for safety concern "Safety in pregnant women (COVID-19 indication)":** Yes, according to the "Summary of risk management plan for (dexamethasone) for treatment of coronavirus disease 2019 (COVID-19)" published on CMDh web site (ref. CMDh/429/2021). The form for follow-up questionnaire is provided in Annex 4 of the RMP.

**Other forms of routine pharmacovigilance activities for both safety concerns:** none

### **III.2 Additional pharmacovigilance activities**

Not applicable as no additional pharmacovigilance activities are proposed or in place for SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection.

### **III.3 Summary Table of additional Pharmacovigilance activities**

Not applicable as no additional pharmacovigilance activities are proposed or in place for SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection.

## **Part IV: Plans for post-authorisation efficacy studies**

Not applicable as there are no planned and on-going imposed post-authorisation efficacy studies on SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection.

## Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

### Risk Minimisation Plan

#### V.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Safety in patients >70 years old and in particular >80 years old (COVID-19 indication)	Routine risk communication: SmPC section 5.1
Safety in pregnant women (COVID-19 indication)	Routine risk communication: SmPC section 4.6 and PL section 2

#### V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

#### V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety in patients >70 years old and in particular >80 years old (COVID-19 indication)	Routine risk minimisation measures: SmPC section 5.1  Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  None  Additional pharmacovigilance activities:  None
Safety in pregnant women (COVID-19 indication)	Routine risk minimisation measures: SmPC section 4.6 and PL section 2  Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  Specific adverse reaction follow-up questionnaires (see Annex 4 of this RMP)  Additional pharmacovigilance activities:

<b>Safety concern</b>	<b>Risk minimisation measures</b>	<b>Pharmacovigilance activities</b>
		None

## **Part VI: Summary of the risk management plan**



# Summary of risk management plan for SOLDESAM s.c. (dexamethasone sodium phosphate)

This is a summary of the risk management plan (RMP) for SOLDESAM s.c. The RMP details important risks of SOLDESAM s.c. how these risks can be minimised, and how more information will be obtained about SOLDESAM s.c.'s risks and uncertainties (missing information).

SOLDESAM s.c.'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SOLDESAM s.c. should be used.

Important new concerns or changes to the current ones will be included in updates of SOLDESAM s.c.'s RMP.

## I. The medicine and what it is used for

SOLDESAM s.c. is authorised for anti-inflammatory corticotherapy and for the treatment of coronavirus disease 2019 (COVID-19) in case of supplemental oxygen therapy (see SmPC for the full indication). It contains dexamethasone sodium phosphate as the active substance and it is given by intravenous route, intramuscular route, intrasynovial route or oral route.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SOLDESAM s.c, together with measures to minimise such risks and the proposed studies for learning more about SOLDESAM s.c 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of SOLDESAM s.c, is not yet available, it is listed under 'missing information' below.

## ***II.A List of important risks and missing information***

Important risks of SOLDESAM s.c. are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SOLDESAM s.c. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

<b>List of important risks and missing information</b>	
Important identified risks	None
Important potential risks	None
Missing information	<ul style="list-style-type: none"> <li>• Safety in patients &gt;70 years old and in particular &gt;80 years old (COVID-19 indication)</li> <li>• Safety in pregnant women (COVID-19 indication)</li> </ul>

## ***II.B Summary of important risks***

<b>Missing information:</b> Safety in patients >70 years old and in particular >80 years old (COVID-19 indication)	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>SmPC section 5.1</p> <p>Additional risk minimisation measures:</p> <p>None</p>

<b>Missing information:</b> Safety in pregnant women (COVID-19 indication)	
Risk minimisation measures	Routine risk minimisation measures:  SmPC section 4.6 and PL section 2  Additional risk minimisation measures:  None

## ***II.C Post-authorisation development plan***

### **II.C.1 Studies which are conditions of the marketing authorisation**

There are no studies which are conditions of the marketing authorisation or specific obligation of SOLDESAM s.c.

### **II.C.2 Other studies in post-authorisation development plan**

There are no studies required for SOLDESAM s.c.

## Part VII: Annexes

### Table of contents

#### ***Annex 1 – EudraVigilance Interface***

Not applicable.

#### ***Annex 2 – Tabulated summary of planned, ongoing, and completed***

Not applicable.

#### ***Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan***

Not applicable.

#### ***Annex 4 - Specific adverse drug reaction follow-up forms***

Questionnaire applicable only for the missing information "Safety in pregnant women (COVID-19 indication)":

<b><u>Sezione a cura del personale di Farmacovigilanza</u></b>	
<b>Database Case ID:</b> .....	
<b>Caso Retrospektivo</b> <input type="checkbox"/>	<b>Caso prospettico</b> <input type="checkbox"/>
<b>FOLLOW-UP 1</b> <input type="checkbox"/>	<b>FOLLOW-UP 2</b> <input type="checkbox"/> <b>Successivo</b> (specificare il numero) <input type="checkbox"/> .....

<b><u>Informazioni sul Segnalatore</u></b>
<b>Iniziali del Segnalatore:</b> .....
<b>Qualifica del Segnalatore</b> (paziente, medico, farmacista ecc.): .....

<b><u>Informazioni sulla madre</u></b>	
<b><i>Informazioni generali</i></b>	
<b>Iniziali:</b> ....	<b>Data di nascita/ età:</b> .....
<b>Peso (Kg):</b> .....	<b>Altezza (Cm):</b> .....
<b><i>Gravidanze precedenti</i></b> (compilare solo se presenti)	

<p><b>Numero precedenti gravidanze:</b>.....</p> <p><b>Esito gravidanze precedenti:</b> .....</p> <p>.....</p> <p><b>Complicazioni rilevate durante le precedenti gravidanze:</b> .....</p> <p>.....</p> <p><b>Anomalie fetali o neonatali rilevate durante le precedenti gravidanze:</b> .....</p> <p>.....</p> <p>.....</p>
<p><b><i>Storia medica e condizioni concomitanti</i></b></p>
<p><b>Malattie / Interventi subiti prima della gravidanza:</b> .....</p> <p>.....</p> <p><b>Storia familiare di anomalie congenite, ritardi nello sviluppo:</b> .....</p> <p>.....</p> <p><b>Malattie concomitanti manifestate durante la gravidanza:</b> .....</p> <p>.....</p> <p><b>Condizioni concomitanti durante la gravidanza:</b></p> <p>Fumo: <input type="checkbox"/>No    <input type="checkbox"/>Sì</p> <p>Alcool: <input type="checkbox"/>No    <input type="checkbox"/>Sì</p> <p>Droghe: <input type="checkbox"/>No    <input type="checkbox"/>Sì</p>
<p><b><i>Gravidanza attuale</i></b></p>
<p><b>Data dell'ultimo ciclo mestruale:</b>.....</p> <p><b>Data del parto prevista:</b>.....</p> <p><b>Numero di feti:</b> .....</p> <p><b>Trattamenti per l'infertilità:</b> <input type="checkbox"/>No    <input type="checkbox"/>Sì (Se sì, specificare quali).....</p> <p>.....</p> <p><b>Test sierologici effettuati (riportare anche gli esiti):</b>.....</p> <p>.....</p> <p>.....</p> <p><b>Test pre-natali effettuati (riportare anche gli esiti):</b>.....</p> <p>.....</p> <p>.....</p>

**Parto** (compilare solo se il parto è già avvenuto)**Tipologia di parto** (es. parto naturale, cesareo):.....**Data del parto:**.....**Esito della gravidanza:**☐ nato vivo                      ☐ aborto                      ☐ gravidanza ectopica☐ gravidanza molare      ☐ morte del feto in stadio avanzato della gravidanza☐ parto pretermine (specificare durata del periodo gestazionale e contesto).....

.....

**Complicazioni** (es. sofferenza fetale): .....

.....

**Prodotti assunti durante la gravidanza****Tipologia prodotti assunti durante la gravidanza inclusi gli integratori:**☐ farmaco/i                      ☐ integratore/i                      ☐ dispositivo/i medico/i                      ☐ altro**1) Nome del prodotto o del principio attivo** .....☐ **prodotto** sospetto                      ☐ **prodotto** concomitante**Dosaggio:** ..... **Via di somministrazione:** .....**Frequenza di somministrazione:** ..... **Periodo di assunzione:** .....**Periodo gestazionale al momento dell'esposizione al prodotto** (espresso in settimane + giorni e specificare se misurato dall'ultimo ciclo mestruale o dall'ecografia):.....

.....

**Indicazione per cui il prodotto è stato assunto:** .....**2) Nome del prodotto o del principio attivo** .....☐ **prodotto** sospetto                      ☐ **prodotto** concomitante**Dosaggio:** ..... **Via di somministrazione:** .....**Frequenza di somministrazione:** ..... **Periodo di assunzione:** .....**Periodo gestazionale al momento dell'esposizione al prodotto** (espresso in settimane + giorni e specificare

se misurato dall'ultimo ciclo mestruale o dall'ecografia): .....

.....

**Indicazione per cui il prodotto è stato assunto:** .....

**3) Nome del prodotto o del principio attivo .....**☐ **prodotto** sospetto☐ **prodotto** concomitante**Dosaggio:** ..... **Via di somministrazione:** .....**Frequenza di somministrazione:** ..... **Periodo di assunzione:** .....**Periodo gestazionale al momento dell'esposizione al prodotto** (*espresso in settimane + giorni e specificare se misurato dall'ultimo ciclo mestruale o dall'ecografia*): .....**Indicazione per cui il prodotto è stato assunto:** .....**4) Nome del prodotto o del principio attivo .....**☐ **prodotto** sospetto☐ **prodotto** concomitante**Dosaggio:** ..... **Via di somministrazione:** .....**Frequenza di somministrazione:** ..... **Periodo di assunzione:** .....**Periodo gestazionale al momento dell'esposizione al prodotto** (*espresso in settimane + giorni e specificare se misurato dall'ultimo ciclo mestruale o dall'ecografia*): .....**Indicazione per cui il prodotto è stato assunto:** .....**Informazioni sul neonato** (*non compilare in caso di parto pre-termine, aborto spontaneo, morte del feto in fase avanzata della gravidanza*)**Data di nascita:** .....**Periodo gestazionale alla nascita:** .....**Sesso del neonato:** ☐ M ☐ F**Dismaturità** ☐ Sì ☐ No**Peso alla nascita (Kg):** .....**Altezza alla nascita (cm):** .....**Circonferenza della testa (cm):** .....**Esami neonatali effettuati** (*riportare gli esiti*): .....**Condizioni alla nascita** (*incluso l'Apgar score a 1 e 5 minuti, trasferimento in unità di terapia intensiva*): .....**Patologie neonatali e terapie somministrate per tali patologie:** .....**Malformazioni/anomalie diagnosticate alla nascita:** .....

.....

**Informazioni sul neonato** *(compilare solo per parto gemellare) (non compilare in caso di parto pre-termine, aborto spontaneo, morte del feto in fase avanzata della gravidanza)*

**Data di nascita:**..... **Periodo gestazionale alla nascita:**.....

**Sesso del neonato:** ☐ M ☐ F **Dismaturità** ☐ Sì ☐ No

**Peso alla nascita (Kg):**..... **Altezza alla nascita (cm):**.....

**Circonferenza della testa (cm):**.....

**Esami neonatali effettuati** *(riportare gli esiti):*.....

.....

**Condizioni alla nascita** *(incluso l'Apgar score a 1 e 5 minuti, trasferimento in unità di terapia intensiva):* .....

.....

.....

**Patologie neonatali e terapie somministrate per tali patologie:** .....

.....

**Malformazioni/anomalie diagnosticate alla nascita:** .....

.....

**Informazioni sul feto** *(compilare in caso di parto pre-termine, aborto spontaneo, morte del feto in fase avanzata della gravidanza)*

**Motivo di terminazione della gravidanza:**

☐ parto pre-termine ☐ aborto spontaneo ☐ morte del feto in fase avanzata della gravidanza

**Periodo gestazionale alla terminazione della gravidanza:**.....

**Test di laboratorio e visita obiettiva del feto alla terminazione della gravidanza** *(riportare anche gli esiti):* .....

.....

**Patologie riscontrate nel feto alla terminazione della**

**gravidanza:** .....

.....



**Informazioni sul feto** (compilare solo per parto gemellare e in caso di parto pre-termine, aborto spontaneo, morte del feto in fase avanzata della gravidanza)

**Motivo di terminazione della gravidanza:**

☐ parto pre-termine      ☐ aborto spontaneo      ☐ morte del feto in fase avanzata della gravidanza

**Periodo gestazionale alla terminazione della gravidanza:** .....

**Test di laboratorio e visita obiettiva del feto alla terminazione della gravidanza** (riportare anche gli

esiti): .....

**Patologie riscontrate nel feto alla terminazione della**

**gravidanza:** .....

.....

**Informazioni sul padre** (compilare solo se influente)

**Iniziali:** ..... **Data di nascita / età:** .....

**Occupazione:** .....

**Storia medica:**.....

.....

**Storia familiare di anomalie congenite, ritardi nello sviluppo:** .....

.....

**Esposizione a farmaci in concomitanza della fecondazione** (indicare per ogni esposizione la data o il periodo di esposizione):.....

.....

**Annex 5 - Protocols for proposed and on-going studies in RMP part IV**

Not applicable.

**Annex 6 - Details of proposed additional risk minimisation activities (if applicable)**

Not applicable.

**Annex 7 - Other supporting data (including referenced material)**

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5. Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. *Neuropharmacology*. 2019 Feb;145(Pt B):230-246. doi: 10.1016/j.neuropharm.2018.08.004. Epub 2018 Aug 4. PMID: 30086289; PMCID: PMC6309515.
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7. <https://bestpractice.bmj.com/topics/en-gb/3000201/epidemiology>
8. Stokum JA, Gerzanich V, Simard JM. Molecular pathophysiology of cerebral edema. *J Cereb Blood Flow Metab*. 2016 Mar;36(3):513-38. doi: 10.1177/0271678X15617172. Epub 2015 Nov 16. PMID: 26661240; PMCID: PMC4776312

### ***Annex 8 – Summary of changes to the risk management plan over time***

Not applicable as this is the first RMP submission for SOLDESAM s.c. 4,37 mg/1 ml, oral solution – solution for injection.