VI.2 Elements for a Public Summary

This is a summary of the risk management plan (RMP) for Dexamethasone Kabi 4 mg/ ml solution for injection, which details the measures to be taken in order to ensure that the medicine is used as safely as possible. This RMP summary should be read in conjunction with the product information for Dexamethasone Kabi 4 mg/ ml solution for injection.

VI.2.1 Overview of Disease Epidemiology

This product contains the active substance dexamethasone sodium phosphate. Dexamethasone sodium phosphate is a glucocorticosteroid, which has anti-inflammatory and immunosuppressant activities. It is used in the treatment of acute conditions in which oral steroid treatment is not feasible, such as:

- Shock (e.g. haemorrhagic, traumatic, surgical or septic origin)
- Cerebral oedema associated with cerebral neoplasm
- Inflammatory diseases of joints and soft tissue such as rheumatoid arthritis
- Short term management of acute self-limited allergic conditions such as angioneurotic oedema or acute exacerbations of chronic allergic disorders such as bronchial asthma or serum sickness.

Accidental injuries remain the leading cause of death in individuals aged 1-44 years (National Center for Injury Control and Prevention). Hemorrhagic shock is a leading cause of death among trauma patients (Cocchi et al., 2007). Septic shock has a crude mortality rate of 45% (Lefering and Neugebauer, 1995) and claims the lives of 90 000 people each year in the USA alone. Patients having severe sepsis or in septic shock were found to have occult or unrecognized adrenal insufficiency; incidence may be as high as 28% in seriously ill patients.

The incidence of metastatic brain tumors exceeds that of primary brain tumors, accounting for 50% of total brain tumors and for as many as 30% of tumors seen on imaging studies alone. An estimated 100,000 new cases are diagnosed per year in the United States; about 60% of patients are aged 50-70 years. More than 20% of patients with systemic disease have brain metastasis on autopsy. About 15% of patients with cancer present with neurologic symptoms before their systemic cancer is diagnosed. Among them, 43-60% have an abnormal chest radiograph suggestive of bronchogenic primary or other metastases to the lung. In 9%, the CNS is the only site of spread. About 10% of patients with proven metastatic disease have no identifiable primary source. Dexamethasone is the treatment of choice in case of cerebral edema. It has the least mineralocorticoid effect of all steroids and is less likely than other steroids to be associated with infection or cognitive dysfunction (Centers for Disease Control and Prevention).

The true incidence of anaphylaxis is unknown. Some clinicians reserve the term for the full-blown syndrome, whereas others use it to describe milder cases. The frequency of anaphylaxis is increasing, and this has been attributed to the increased number of potential allergens to which people are exposed. A review concluded that the lifetime prevalence of anaphylaxis is 1-2% of the population as a whole (Lieberman 2008).

Internationally, the prevalence of Rheumatoid Arthritis (RA) is believed to range from 0.4 to 1.3%. In 2005, an estimated 1.5 million (0.6%) of US adults age ≥ 18 had RA. The prevalence of RA, at least among women, may be increasing. The Rochester Epidemiology Project provided the most recent US data on the incidence of RA. In 1995-2007, 41 per 100,000 people were diagnosed with RA annually. Incidence rose with age (e.g., 8.7 per 100,000 people among those aged 18-34 years compared with 54 per 100,000 among those age ≥ 85 years) and peaked at age 65-74 years (89 per 100,000); all estimates age-adjusted to 2000 US population. From 1995 to 2007, rates increased by 2.5% each year among women but there was a small decrease (0.5%) among men. In longitudinal study of RA in the Rochester Epidemiology Project, incidence among women and men was highest at the beginning of the project in 1955, but declined to its lowest in the late 1980s and early 1990s (Centers for Disease Control and Prevention).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (Covid-19), emerged in China in late 2019 from a zoonotic source. The majority of Covid-19 cases either are asymptomatic or result in only mild disease. However, in a substantial percentage of patients, a respiratory illness requiring hospital care develops, and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support. Among patients with Covid-19 who have been admitted to hospitals in the United Kingdom, the case fatality rate has been approximately 26%, a percentage that has increased to more than 37% among patients who were undergoing invasive mechanical ventilation. Although remdesivir has been shown to shorten the time until recovery in hospitalized patients, no therapeutic agents have been shown to reduce mortality. The pathophysiological features of severe Covid-19 are dominated by an acute pneumonic process with extensive radiologic opacity and, on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis.

Dexamethasone was first considered a potential treatment for COVID-19 because of its ability to reduce inflammation, which plays an important role in the disease process in some patients who have been admitted to hospital with COVID-19. [8]

VI.2.2 Summary of Treatment Benefits

Dexamethasone Kabi 4 mg/ ml solution for injection can be used for all forms of general and local glucocorticoid injection therapy and all acute conditions in which intravenous glucocorticoids may be life-saving.

Dexamethasone is a synthetic adrenocorticoid with approximately a 7 times higher anti-inflammatory potency than prednisolone and 30 times that of hydrocortisone. Dexamethasone has only minor mineralocorticoid activities and does therefore, not induce water and sodium retention.

Dexamethasone sodium phosphate injection has a rapid onset but short duration of action when compared with less soluable preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steriod therapy.

A plenty of data is available in the literature about using and dosing of dexamethasone administered IM or IV for the following indication:

- Shock: haemorrhagic, traumatic, surgical or septic origin
- Cerebral oedema associated with cerebral neoplasm or life-threatening cerebral oedema
- Short term management of acute self-limited allergic conditions such as angioneurotic oedema or acute exacerbations of chronic allergic disorders such as bronchial asthma or serum sickness.

The duration of therapy is dependent on the clinical response of the patient and as soon as improvement is indicated, the dosage should be adjusted to the minimum required to maintain the desired clinical response. Withdrawal of the drug on completion of therapy should be gradual.

Dosage for intraarticular and soft tissue injection varies with the degree of inflammation and the size and location of the affected area.

Regarding COVID 19, the RECOVERY trial (Randomised Evaluation of COVid-19 thERapY, www.recoverytrial.net) is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial which evaluated the effects of potential treatments in patients hospitalised with COVID-19 at 176 National Health Service (NHS) hospital organizations in the United Kingdom. The study found that mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). 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% versus 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving supplementary oxygen without invasive mechanical ventilation (23.3% versus 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94). There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomisation. No dose adjustment was needed for the elderly, renal and hepatic impaired patients. No significant safety concerns were noted to occur in the RECOVERY study.

These results were further supported by results from a meta-analysis conducted by the WHO (Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group) which looked at data from seven clinical studies (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional studies; n=1703 patients) investigating the use of corticosteroids for the treatment of patients with COVID-19 (678 patients had been randomised to corticosteroids and 1025 to usual care or placebo). The 28-day mortality was lower in patients randomised to corticosteroids: 222 deaths among 678 patients randomised to corticosteroids compared with 425 deaths among 1025 patients randomised to usual care or placebo (summary odds ratio, 0.66; 95% CI, 0.53,-0.82; P<0.001).

After reviewing all these data, the CHMP concluded that the benefit-risk balance of the use of dexamethasone in COVID-19 patients is positive and a beneficial effect on day 28 mortality has been demonstrated. Consequently, the EMA endorsed in September 2020 the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. [9, 10]

VI.2.3 Unknowns relating to treatment benefits

Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.

Dexamethasone has been used 'off–label' to treat and prevent chronic lung disease in preterm infants. Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/hg twice daily. Trials have suggested an association between the use of dexamethasone in preterm infants and the development of cerebral palsy. In view of this possible safety concern, an assessment of the risk: benefit should be made on an individual patient basis.

Treatment of elderly patients, particularly long-term, should be planned, bearing in mind the more serious consequences in old age. Such effects include osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection, thinning and fragility of the skin. Close clinical supervision is required to avoid life-threatening reactions.

However, for the following patient groups the benefits of dexamethasone does not outweigh the risks and the product should not be used in patients with:

- Hypersensitivity to dexamethasone or any of the excipients. Severe anaphylactoid reactions have occurred after administration of parenteral corticosteroids, particularly in patients with history of allergy. Appropriate precautions should be taken prior to administration.
- Systemic infections: unless considered to be life-saving systemic administration of corticosteroids are generally contraindicated in patients with systemic infections (unless specific anti-infective therapy is employed).

There is a lack of evidence to support the prolonged use of corticosteroids in septic shock. Although they may be of value in the early treatment, the overall survival may not be influenced.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Psychiatric disorders	Many different psychiatric disorders have been reported with dexamethasone, such as depression, somnolence, latered mood, euphoria, insomnia, anxiety, irritability and agitation. Risks may be higher with high doses/systemic exposure although dose levels do not allow prediction of the onset, type, severity or duration of reactions.	Caution is required when considering the use of dexamethasone in patients with existing or previous severe psychiatric disorders. Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting the treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.
Hypothalamic-pituitary-adrenal suppression	Treatment with corticosteroids may increase the risk of a condition called adrenal suppression (HPA axis suppression) which may lead to a condition called Cushing's disease. Symptoms of Cushing's disease include upper body obesity, rounded face, increased fat around the neck, thinning arms and legs, fatigue, weakness, high blood pressure, and mood disorders.	The lowest effective dose of corticosteroid should be used to control the condition under treatment for the minimum period. Withdrawal of corticosteroids after prolonged therapy must, therefore, be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.
Growth retardation in infancy, childhood and adolescence	Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible.	Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamic-pituitary-adrenal axis and growth retardation, treatment should be limited, where possible, to a single dose on alternate days.

Infections	Increased susceptibility to and severity of infection with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis occur with dexamethasone alone in a majority of patients.	Suppression of the inflammatory response and the immune function increases the susceptibility to infections and their severity. The clinical presentation may be atypical and serious infections, such as septicaemia and tuberculosis, may be masked and may reach an advanced stage before being recognised. During treatment, patients should be closely monitored for the appearance of infections, in particular pneumonia (lung infection). Patients should be informed of the signs and symptoms of pneumonia and be advised to seek medical attention in case of their appearance. Patients must avoid contact with people with chickenpox or measles. Exposed patients should be advised to seek medical attention without delay. Prior to intraarticular injection the joint fluid should be examined to exclude a septic process.
Hypersensitivity reactions	Severe anaphylactoid reactions have occurred after administration of parenteral corticosteroids, particularly in patients with history of allergy.	Appropriate precautions should be taken prior to administration. Hypersensitivity to the active substance or to any of the excipients listed in the SmPC and Package leaflet should be contraindicated.
Interaction with live attenuated vaccines	Patients with systemic dexamethasone treatment are more likely to develop vaccine-related illnesses	Live vaccines should not be given to individuals with impaired immune responsiveness under dexamethasone treatment.
Visual disturbances	Visual disturbances, e.g. chorioretinopathy, blurred vision, have been reported with systemic and topical corticosteroid use.	Patients and/or carers should be warned that visual disturbances may occur with systemic steroids. Patients/carers should be encouraged to seek an ophthalmologist advice if symptoms develop.

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Drug interactions with anticoagulants	The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of prothombin time or INR is required to avoid spontaneous bleeding.
Interactions with non-steroidal anti-inflammatory drugs	The incidence of gastro-intestinal ulceration is increased in patients receiving concomitant non-steroidal anti-inflammatory drugs and corticosteroids.
Teratogenic effect	There are no or limited data from the use of dexamethasone in pregnant women. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects 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 man.
Use in patients with: liver diseases, renal failure, cardiovascular disorders, osteoporosis, diabetes mellitus, patients with affective	Extreme caution should be exercised in the treatment of patients with such conditions and frequent patient monitoring is necessary. Treatment of elderly patients, particularly long-term, should be planned, bearing in mind the more serious consequences in old age. Such effects include osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to

disorders, glaucoma, peptic ulceration or previous corticosteroid induced myopathy.	infection, thinning and fragility of the skin. Close clinical supervision is required to avoid life-threatening reactions.
Medication error	A dosing chart in SPC and the Package Leaflet is to be used only by healthcare professionals for the administration of Dexamethasone Kabi 4 mg/ml solution. All doses are expressed as **mg** dexamethasone phosphate and required volume of product as **ml.**

Missing information

Risk	**What is known**
Off-label use (to treat and prevent chronic lung disease in preterm infants)	Dexamethasone has been used 'off–label' to treat and prevent chronic lung disease in preterm infants. Clinical trials have shown a short term benefit in reducing ventilator dependence but no long term benefit in reducing time to discharge, the incidence of chronic lung disease or mortality. Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/hg twice daily. Recent trials have suggested an association between the use of dexamethasone in preterm infants and the development of cerebral palsy. In view of this possible safety concern, an assessment of the risk: benefit should be made on an individual patient basis.
Pregnant and lactating women	Pregnancy The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects 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 man. See also section 5.3 of the SmPC. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to the corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state. There is evidence of harmful effects on pregnancy in animals. Infants born to mothers who have received substantial doses of corticosteroids during the pregnancy should be carefully observed, for signs of adrenal insufficiency. Patients with pre-eclampsia or fluid retention require close monitoring. Breast-feeding Corticosteroids may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression. Suppression of growth or other adverse effects may occur.
Paediatric population	Dosage requirements are variable and may have to be changed according to individual need. Usually 200 micrograms/kg to 400 micrograms/kg (0.05 ml/kg to 0.1 ml/kg) of body weight daily. Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamic-pituitary-adrenal axis and growth retardation, treatment should be limited, where possible, to a single dose on alternate days. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.

VI.2.5 Summary of risk minimisation measures by safety concern

Dexamethasone Kabi 4 mg/ml solution for injection has a Summary of Product Characteristics (SPC) which provides physicians, nurses, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.