VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an immune system disease that has different manifestations and follows a “come and go” course of disease. More than 90% of cases of SLE occur in women, frequently starting at childbearing age.

The annual number of new cases of SLE averages 5 cases per 100,000 population and the reported rate of occurence ranges from 52 cases per 100,000 population in the USA. More than 90% of cases of SLE occur in women.

Rate of death in patients with SLE has decreased over the past few decades. Prior to 1955, the

5-year survival rate in SLE was less than 50%; currently, the average 10-year survival rate exceeds 90% in the USA. Previously, death was due to the disease itself; currently, death is often a result of medication side effects (eg, fatal infections in individuals receiving potent immunosuppressive medications) or heart and vessel disease.[1]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. An external trigger (eg, cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to enlargement of the joint-lining membrane and chronic joint inflammation along with the potential for manifestations in other organs, is theorized to occur in genetically susceptible people.

Worldwide, the annual number of new cases of RA is approximately 3 cases per 10,000 population, and the occurence is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years.

RA is associated with risk of heart and vessel disease. The leading cause of excess dying in

RA is heart and vessel disease, followed by infection, lung disease, and malignancies. The overall rate of death in patients with RA is reportedly 2.5 times higher than that of the general age-matched population.[4]

Juvenile idiopathic arthritis

Juvenile rheumatoid arthritis (JRA) is the most common chronic rheumatologic disease in children and is one of the most common chronic diseases of childhood. The cause is unknown, and the genetic component is complex, making clear distinctions between the various subtypes difficult.

A study from Germany found a rate of occurence of 20 cases per 100,000 population, with annual number of new cases of 3.5 cases per 100,000 population.

Disease-associated death for JIA is difficult to quantify, but it is estimated to be less than 1% in Europe.[7]

Polyarteritis nodosa

Polyarteritis nodosa is a systemic inflammation of blood vessels characterized by necrotizing inflammatory lesions that affect medium-sized and small muscular arteries, preferentially where vessels divide in two branches, resulting in microaneurysm formation, aneurysmal rupture with hemorrhage, thrombosis, and, consequently, organ ischemia or infarction. Polyarteritis nodosa (PAN) is a rare disease, with number of new cases of about 3-4.5 cases per 100,000 population annually. Depending on the definitions used, the annual estimated occurence of PAN ranges from 1.6 cases per million in south Sweden to 4.6 cases per million in England to 30.7 cases per million adults in Paris, France.

When left untreated, the 5-year survival rate of PAN is 13%. Nearly half of patients die within the first 3 months of onset.

Bronchial asthma

Asthma is a long term disease of swelling of the airways of the lungs. Asthma is a common chronic disease worldwide and affects approximately 24 million persons in the United States. It is the most common chronic disease in childhood, affecting an estimated 7 million children. The pathophysiology of asthma is complex and involves airway inflammation, off-and-on airflow obstruction, and bronchial hyperresponsiveness.

Rate of occurence is increasing. Up to 15% of children and young adults are affected.

Worldwide, approximately 300 million people have asthma.

International asthma death rate is reported as high as 0.86 deaths per 100,000 persons in some countries.[6, 24]

Croup

Croup is a common, primarily pediatric viral respiratory tract illness. As its alternative names, laryngotracheitis and laryngotracheobronchitis, indicate, croup generally affects the larynx (voice box) and trachea (windpipe), although this illness may also extend to the bronchi. It is the most common etiology for hoarseness, cough, and onset of acute high-pitched breath sound in children with fever. Symptoms of croup may be absent, mild, or marked. The vast majority of children with croup recover without consequences or sequelae; however, it can be life-threatening in young infants.

In North America, number of new cases annually peaks in the second year of life, at 5-6 cases per 100 children. Although uncommon after age 6 years, croup may be diagnosed in the preteen and adolescent years (age 12-15 y), and rarely in adults.[12]

Erythroderma

Erythroderma is an inflammatory skin disease with redness of skin and scaling that affects nearly the entire skin surface.

Pemphigus vulgaris

Pemphigus vulgaris is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membranes. It is mediated by circulating autoantibodies directed against keratinocyte

(the predominant cell type in the epidermis, the outermost layer of the skin)cell surfaces. A potentially life-threatening disease, it has a mortality rate of approximately 5-15%.

Pemphigus vulgaris number of new cases varies from 0.5-3.2 cases per 100,000 population. Up to 10% of patients may die either due to complications of the disease or from side-effects of the treatment.[2, 11]

Tuberculous meningitis

Tuberculosis (TB) is a contagious airborne disease that typically affects the lungs. TB is caused by a bacterium called Mycobacterium tuberculosis. In 2 % of cases the bacterium travels to the membranes surrounding the brain and spinal cord (the meninges). Infection of the meninges can result in the development of a life-threatening condition known as tuberculous meningitis. Globally, more than 1 in 3 individuals is infected with tuberculosis. According to the WHO, there were 8.8 million incident cases of tuberculosis worldwide in 2010, with 1.1 million deaths from tuberculosis among HIV-negative persons and an additional 0.35 million deaths from HIV-associated tuberculosis.[17, 24, 28]

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura is a decrease in the number of circulating platelets in the absence of toxic exposure or a disease associated with a low platelet count.

The number of new cases in adults is 66/1,000,000 per year and in children 10-40/1,000,000 per year. The mortality rate from hemorrhage (the most serious complication) is approximately 1% in children and 5% in adults.

Cerebral oedema

Cerebral oedema is defined as an increase in brain water content (above the normal brain water content of approximately 80%) and invariably a response to a primary brain insult. It is commonly observed in a variety of brain injury paradigms.

Leukaemia

Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system. Some patients die rapidly within 2-3 years of diagnosis, because of complications from disease, but most patients live 5-10 years.

The annual number of new cases of leukaemia is estimated around 10/100,000 per year worldwide. [22, 24]

Hodgkin's disease

Hodgkin's lymphoma (formerly known as Hodgkin's disease) is a cancer of the lymphatic system, which is part of your immune system.

The annual number of new cases of Hodgkin's disease is estimated around 10/100,000 per year worldwide. Patient prognosis is largely based on the stage of the disease and various prognostic factors, which may be defined differently across various major cooperative groups [21]

Non-Hodgkin's lymphoma

The non-Hodgkin lymphoma is a diverse group of blood cancers that includes any kind of lymphoma except Hodgkin's lymphoma.

Non-Hodgkin's lymphoma is the most common hematopoietic tumor, representing approximately 4% of all cancer diagnoses and ranking seventh in frequency among all cancers. Non-Hodgkin's lymphoma is more than 5 times as common as Hodgkin disease. The 5-year relative survival rate of patients with Non-Hodgkin's lymphoma is approximately 63%. The survival rate has steadily improved over the last 2 decades, thanks to improvements in medical and nursing care, the advent of novel therapeutic strategies (ie, monoclonal antibodies), validation of biomarkers of response, and the implementation of tailored treatment.[20]

Palliative treatment of neoplastic diseases

Palliative care is specialized medical care for people with serious illnesses. This type of care is focused on providing patients with relief from the symptoms, pain, and stress of a serious illness.

The American Cancer Society estimates the number of new diseases and deaths from neoplasms in the United States every year. 1 596 670 new cases and 571 590 deaths were estimated in 2011, while in Poland 131 063 new cases and 93 060 deaths were observed in 2008.[18, 19]

Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy

Two of the most common side effects of chemotherapy are nausea and vomiting. These side effects have a significant impact on quality of life and can interfere with the ability to deliver intensive care. Fortunately, improvements in supportive and adjunctive care have also been attained, and current treatments for nausea and vomiting are effective in mitigating these adverse effects in most patients.

The frequency of nausea and vomiting is related to the risk of the particular chemotherapeutic agent to cause emesis or combination of drugs being administered.[16]

Prevention and treatment of postoperative vomiting

Postoperative nausea and vomiting, defined as nausea and/or vomiting occur within 24 hours after surgery and affect between 20% and 30% of patients. As many as 70% to 80% of patients are at high risk and may be affected.[13]

Multiple myeloma

Multiple myeloma is a cancer of the plasma cells in the bone marrow.

The annual number of new cases of multiple myeloma is estimated around 4/100,000 per year worldwide. Multiple myeloma survival ranges from 1 year to more than 10 years. Median survival in unselected patients with multiple myeloma is 3 years.[8, 24]

Myositis

Myositis refers to any condition causing inflammation in muscles. Weakness, swelling, and pain are the most common myositis symptoms. Myositis causes include infection, injury, autoimmune conditions, and drug side effects. Treatment of myositis varies according to the cause. [5]

Metastatic spinal cord compression

The spinal cord is a long bundle of nerves which stretches from the brain to the lower part of the back.

Spinal cord compression happens when there is pressure on the spinal cord. This pressure may be caused by a cancer that started in, or has spread into, the bones of the spine. Between 5 and 10 out of 100 people with cancer (5 to 10%) develop spinal cord compression. Most of these are due to cancer spreading to the spine from another part of the body (metastases). All types of cancer can spread to the bones of the spine. But it is more common in cancers of the prostate, breast or lung, and lymphoma.[30]

VI.2.2 Summary of treatment benefits

Dexamethasone is a synthetic glucocorticoid. Glucocorticoids are hormones produced by the cortex of adrenal glands. The medicine has anti-inflammatory, analgesic and anti-allergic effects, and suppresses the immune system.

Dexamethasone 0,5 mg tablets:

Dexamethasone 0.5 mg tablets are used in diseases that require systemic treatment with glucocorticoids. These include, depending on the type and severity:

-Swelling of the brain caused by brain tumours, neurosurgery, bacterial inflammation of the lining of the brain (meningitis), brain abscess

-Severe acute asthma attack

-Initial treatment of extensive acute severe skin diseases, such as erythroderma, pemphigus vulgaris, acute eczema

-Treatment of rheumatic systemic diseases (rheumatic diseases which can affect internal organs), such as systemic lupus erythematosus

-Severely progressive form of active rheumatic joint inflammation (rheumatoid arthritis), e.g. forms that quickly lead to joint destruction and/or when tissue outside the joints is affected

-Severe infections with intoxication-like conditions (e.g. in tuberculosis, typhoid fever), only with appropriate anti-infective therapy

-Supportive treatment in malignant tumours

-Hormone replacement therapy: in reduced adrenal function or failure of adrenal function (adrenogenital syndrome) in adulthood.

Dexamethasone 4 mg, 8 mg tablets:

Dexamethasone Krka is recommended for the treatment of rheumatic and autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid artritis, juvenil idiopathic arthritis, polyartheritis nodosa), diseases of respiratory tract (e.g. bronhial asthma, croup), skin (e.g. erythroderma, pemphigus vulgaris), tuberculous meningitis only in conjunction with anti-infective therapy, diseases of blood (e.g. idiopathic thrombocytopenic purpura in adults), cerebral oedema, treatment of symptomatic multiple myeloma, acute lymphocytic leukemia, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products, palliative treatment of neoplastic diseases, prophylaxis and treatment of nausea and womiting caused by chemotherapy and prevention and treatment of vomiting after operation, within antiemetic treatment.

Dexamethasone 20 mg, 40 mg tablets:

Dexamethasone Krka is recommended for the treatment of rheumatic and autoimmune diseases (e.g. myositis), skin (e.g. pemphigus vulgaris), diseases of blood (e.g. idiopathic thrombocytopenic purpura in adults), treatment of symptomatic multiple myeloma, acute lymphocytic leukemia, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products, palliative treatment of neoplastic diseases, prophylaxis and treatment of nausea and womiting caused by chemotherapy, within antiemetic treatment.

VI.2.3 Unknowns relating to treatment benefits

The substance dexamethasone has been in use for many years. Many studies have been performed and a lot of data have been obtained from the patients treated with this drugs.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity including anaphylaxis to dexamethasone or any excipients	This medication may cause allergic reactions as all medicines can.	Yes, by monitoring for early symptoms and avoiding the drugs you are already known to be allergic of. Please tell your doctor if you are undergoing or are planning to undergo desensitisation therapy.
Risk of opportunistic infection, aggravation or masking of signs of infection: impaired immune response to vaccines	This medication may cause increased risk of infection due to immunosuppression. It can also impair immune response to vaccines.	As in the majority of other side effects of glucocorticoids, the risk of infections depends on the dose of the glucocorticoid and duration of treatment. The risk is lower in intermittent therapy. If you are at risk you should receive immunoprophylactic protection during glucocorticoid treatment. If you develop an infection whilst on this medicine you should talk to your doctor. If you require a vaccination (particularly with 'live virus' vaccines) whilst taking or when you have finished taking dexamethasone, you should inform the person treating you that you are taking or have taken steroids.
Reduced glucose tolerance	This medication may cause elevation of blood sugar.	Yes, by monitoring and treatment of increased blood glucose.
Adrenal suppression (associated with long-term use in children)	This medication may cause adrenal suppression. This can lead to inhibition of growth in children.	If a child is taking this medicine, it is important that the doctor monitors their growth and development at frequent intervals. Long term treatment should be prescribed with caution (indication should be very strongly presented).
Osteoporosis, especially in patients at risk	This medication may cause osteoporosis.	Prevention of osteoporosis consists of sufficient calcium and vitamin D intake and physical activity. You should consider medical treatment in the event of pre-existing osteoporosis.
Gastrointestinal ulcers or bleeding, intestinal perforation	This medication may cause gastrointestinal ulcers or bleeding, intestinal perforation.	Do not take dexamethasone if you have stomach or duodenal ulcer. Prevention of events consists of prophylactic treatment.

Cataract, glaucoma or corneal ulcer	This medication may cause cataract, glaucoma or corneal ulcer.	For prevention of glaucoma, routine measurement of intraocular pressure and periodic ophthalmologic examinations of patients treated with glucocorticoids are recommended.
Exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency, corticosteroid withdrawal syndrome upon interruption/discontinuation of long-term glucocorticoid administration	Discontinuation of medicine may cause exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency, corticosteroid withdrawal syndrome upon interruption/discontinuation of long-term glucocorticoid administration	For prevention glucocorticoid doses should be gradually reduced and treatment should be discontinued gradually.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Cardiovascular complications at high risk patients	Use of dexamethasone can elevate blood pressure, impair glucose tolerance, cause dyslipidaemia and imbalances in

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Risk	**What is known (Including reason why it is considered a potential risk)**
	thrombosis and fibrinolysis. These are risk factors that can lead to additional impairment of the cardiovascular system in patients with the pre-existing cardiovascular diseases.
Congenital abnormalities	In animal studies, dexamethasone has been shown to cause birth defects, but proponents of the treatment note that no human birth defects have ever been associated with the treatment, and that it is uncertain whether findings in lab animals translate to humans. Dexamethasone should be prescribed during pregnancy, and particularly in the first trimester, only if the benefit outweighs the risks for the mother and child.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, 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.

The Summary of Product Characteristics and the Package leaflet for Dexamethasone can be found in the Dexamethasone's EPAR page

This medicine has no additional 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

Version	Date (sign off)	Safety concerns	Comment
1.4	13.7.2016	**Important identified risks** • 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 **Important potential risks** • Cardiovascular complications at high risk patients (such as post-infarct myocardial rupture, congestive heart failure) • Congenital abnormalities • **Missing information** Not applicable.	This version was approved as first version of dexamethasone RMP in procedure HU/H/0399/001-004/DC.
2.0 current	15.3.2017	There was no change in important safety concerns.	Version 2.0 arised during procedure of new authorisations from merging 2 RMPs (from well-established use and generic application) for tablets in order to have one RMP. Since Krka has products with dexamethasone for more than 50 years, injection for solution has been also added to cover all the products with the active substance.

2.1	24.7.2017	There was no change in important safety concerns.	Part VI.2.2 has been changed to the previous version, as was approved in version 1.4.
2.2	28.8.2017	There was no change in important safety concerns.	Part VI.2.2 has been corrected to include all strengths.

1.8.2 clean	Dexamethasone
Risk Management System	tablets

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 - SmPC & Package Leaflet

Please see attached document.

Annex 3 - Worldwide marketing authorisation by country (including EEA)

Please see attached document.

Annex 4 - Synopsis of o