VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Prednisolone is generally preferred amongst glucocorticoids for anti-inflammatory and immunosuppressive treatment. There are three main areas where prednisolone is prescribed and they are described below:

Diseases in which appear swelling, redness, pain and heat; aspects of the immune system (Inflammatory and immunologic conditions-IMID)

Disease that primarily affects joints (Rheumatoid Arthritis-RA)[Fejl! Bogmærke er ikke defineret.]

Studies of RA conducted in Northern European and North American countries indicate that up to 1% of the population has RA and that a further 2-5 people per 10,000 in the population will develop the disease each year. RA is not as commonly reported in developing countries, though Native Americans appear to be highly affected by the disease. The incidence of RA is higher in women than in men.

Inflammatory disease of the skeleton, with involvement of peripheral joints and non-joint structures (Ankylosing Spondylitis-AS)

AS primarily affects men before the age of 45 years with up to 1 person per 10,000 in the population being affected. Disease onset is usually between 17 to 35 years of age.[Fejl! Bogmærke er ikke defineret.]

In general, AS is diagnosed more frequently in males than in females (three males for every one female)..

Patients tend to be diagnosed quicker when they experience inflammatory (reaction including swelling, redness and heat) back pain or have a known family history of AS.[Fejl! Bogmærke er ikke defineret.]

Skin lesions including red, scaly patches, moles, and plaques, which usually itch (Psoriasis and Psoriatic Arthritis)[Fejl! Bogmærke er ikke defineret.]

Psoriasis occurs worldwide with about 2% of the North American population being affected. The disease can present at any age; however, the mean age of onset for the first presentation of psoriasis ranges from 15-20 years of age, with a second time occurring at 55-60 years.

Among patients with psoriasis, the prevalence of inflammatory arthritis varies from 6% to 42%.

Group of inflammatory conditions of the colon and small intestine (Inflammatory Bowel Disease-IBD)[Fejl! Bogmærke er ikke defineret.]

The incidence of IBD varies greatly worldwide. However, in traditionally high-incidence areas such as Western European and North American countries, the figures have stabilized or slightly increased. In contrast, low prevalence and incidence rates have historically been reported in other parts of the world, including Eastern Europe, South America, Asia, and the Pacific region. Recent trends, however, also indicate a change in the epidemiology in these areas as they are now reporting a progressive increase in the incidence of IBD. It is also important to note that IBD emerges in developing countries.[Fejl! Bogmærke er ikke defineret.]

The male-to-female ratio is approximately 1:1 for ulcerative colitis and Crohn disease, with females having a slightly greater incidence. Both diseases are most commonly diagnosed in young adults (ie, late adolescence to the third decade of life).[Fejl! Bogmærke er ikke defineret.]

Condition which causes narrowing of the airways (Acute Asthma)

Asthma affects 5-10% of the population or an estimated 23.4 million persons, including 7 million children. Asthma affects an estimated 300 million individuals worldwide. Annually, the World Health Organization (WHO) has estimated that 15 million disability-adjusted life-years are lost and 250,000

asthma deaths are reported worldwide. Asthma is common in industrialized nations such as Canada, England, Australia, Germany, and New Zealand, where much of the asthma data have been collected. The prevalence rate of severe asthma in industrialized countries ranges from 2-10%.[Fejl! Bogmærke er ikke defineret.]

Asthma predominantly occurs in boys in childhood, with a male-to-female ratio of 2:1 until puberty, when the male-to-female ratio becomes 1:1. Asthma prevalence is greater in females after puberty, and the majority of adult-onset cases diagnosed in persons older than 40 years occur in females. Boys are more likely than girls to experience a decrease in symptoms by late adolescence.[Fejl! Bogmærke er ikke defineret.]

Nonspecific kidney disorder (Nephrotic syndrome)

Nephrotic syndrome occurs worldwide. In the United States, diabetic nephropathy with nephrotic syndrome is most common, at an estimated rate of at least 50 cases per million population. In children, nephrotic syndrome may occur at a rate of 20 cases per million children.[Fejl! Bogmærke er ikke defineret.]

Because diabetes is major cause of nephrotic syndrome, American Indians, Hispanics, and African Americans have a higher incidence of nephrotic syndrome than do white persons.
Nephrotic syndrome occurs more frequently in males than females, as for chronic kidney disease in general.[Fejl! Bogmærke er ikke defineret.]

VI.2.2 Summary of treatment benefits

- One analysis including 20 trials examined the efficacy of corticosteroids in the treatment of inflammation, thickening and ulcerations of the intestines (Crohn's disease-CD) and lesions inflammation of the colon (ulcerative colitis -UC). According to the results of the study, glucocorticosteroids were superior to placebo for UC remission and CD remission reported a statistically significant effect. The author concluded that standard glucocorticosteroids are effective in inducing remission in UC, and may be of benefit in CD.

- One study assessed the effect of immediate administration of (stat) oral prednisolone on the rate of hospitalization in patients with acute bronchial asthma. 259 patients, aged 1-65 years presenting with acute exacerbation of asthma were included to receive a stat dose of oral prednisolone. The results of the study showed that only 37 patients required hospitalisation and further management in the prednisolone group compared to 50 patients in the placebo group. The authors concluded that the prompt use of a single oral dose of prednisolone along with routine bronchodilator therapy can significantly reduce morbidity and need for hospital admission in patients of acute bronchial asthma.

- One study including 20 adult patients with the nephrotic syndrome compared the effects of consecutive eight week courses of treatment of prednisolone in conventional (normal) dosage with low-dose azathioprine+prednisolone combination. Patients were divided in two groups: group A received prednisolone; and group B comprised prednisolone plus azathioprine daily for eight weeks. According to the results of the study, the results were not significantly better than with prednisolone itself and overall were not of great clinical value. Prednisolone was shown effective in these nephrotic syndrome adult patients as excretion of protein in the urine was stopped or significantly reduced with time.

VI.2.3 Unknowns relating to treatment benefits

According to the SmPC, there is limited information regarding prednisolone use in pregnancy and breast-feeding. However, based on current knowledge, there is no indication to suggest that treatment results would be different in any subgroup of the target population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Mental illness (Psychiatric disorders-psychosis, depression, mania without known history, activation of previous psychiatric disorders)	Existing emotional instability or mental illness may be worsened by prednisolone without the affected person being aware of it. Patients treated with prednisolone may develop an extreme sense of well-being (euphoria), mental state characterized by extreme sadness (depression), difficulty in sleeping (insomnia), mood swings or hallucinations. Extremely slowed motor activity, often to the point of being motionless and appearing unaware of ones surroundings (catatonic stupor) may occur very rarely (less than 1 in 10,000 patients)..	Clinicians should be careful with initial exposure to prednisolone, and the risk of mental illness is lower follows dose adjustment (either division or reduction).[i]
Greater risk of infection, including serious infections (Increase in susceptibility and severity of infections)	Patients should be aware about the fact that long-term therapy may increase the risk of fungal or viral infections in the eye. Infections are very common reactions (occurring in more than 1 in 10)	Patients on systemic antifungal agents should not receive prednisolone unless absolutely essential. Similarly, patients on prednisolone should not be vaccinated with live vaccines and should avoid exposure to chickenpox and measles. Any unusual symptoms should be reported immediately to the treating physician as it may be due to a new infection.
Abnormal chemical levels in the blood: e.g –potassium, sodium, calcium; underactive thyroid gland which can cause tiredness or weight gain; change in bone mass,	Patients may develop an increased need for insulin or other medical treatment; hypothyroidism (an underactive thyroid gland which can cause tiredness or	Patients with osteoporosis should be checked for adequate calcium and vitamin D intake and be encouraged to exercise. Diabetics, patients with hypothyroidism and those

Risk	What is known	Preventability
diabetes; high cholesterol, triglycerides and lipoprotein (Metabolism disorders)	weight gain); osteoporosis (thinning of the bone). A negative effect on the way calcium circulates in patients bones could be present. Common reactions which have been reported included (affects 1 to 10 out of 100) reported with use: too low potassium levels (muscle weakness, general weakness and heart rhythm disturbances which may be severe), reduced excretion of salt. Uncommon reactions reported: (affects 1 to 10 users in 1,000): change in bone mass, diabetes (low dose). Rare (affects 1 to 10 users in 10,000): thyroid function dis-order Very rare (affects less than 1 in 10,000) including not known (cannot be estimated from available data): in-creased production of para-thyroid hormone, attacks of porphyria (rare inherited metabolic disorder), changes in certain laboratory tests: low potassium levels, high cholesterol, triglycerides and lipoprotein.	with high cholesterol should be more frequently checked under treatment with prednisolone.
Growth inhibition in children (Growth inhibition in the paediatric population)	Prolonged treatment may reduce the development and growth in infants and children. Reported very common reactions (occurring in more than 1 in 10): growth retardation in children.	Corticosteroids inhibit linear growth. The mechanism of this effect is unknown but may involve a combination of reduced growth hormone production and a direct inhibitory effect on bone and connective tissue. Growth suppression is more likely if

Risk	What is known	Preventability
		steroids are given for more than six months. Apparent slow growth may be more due to a delayed puberty than actual side effects of the corticosteroids. It is important to monitor growth in children undergoing steroid therapy using growth charts. Growth suppression is relieved by alternate day treatment.[ii]
Cushing like Symptoms	Cushing's syndrome (moon face and increased amount of body fat- with continued high doses) is a common reaction (affects 1 to 10 out of 100)	Doctors should inform patients that frequent repeated dosing of prednisolone for a longer period may cause a Cushing-like state.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in pregnancy	Pregnant women, or women planning to have a baby should ask doctor or pharmacist for advice before taking prednisolone. Pregnant women should not normally take prednisolone as. long-term treatment has resulted in slightly reduced birth weight. When used late in pregnancy, the use of prednisolone has been associated with risk of side-effects such as in-creased risk of infection and impaired adrenal function in the fetus.

Missing information

Risk	What is known
Use in lactating mothers	Breast-feeding women should ask doctor or pharmacist for advice before taking prednisolone. Women can still take prednisolone if they are breast-feeding, however they must follow your doctors instructions. The doctor will want to examine the baby's growth and adrenal function during time of treatment. Small amounts of steroids are pre-sent in breast milk.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for prednisolone.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	03-03-2015	Important identified risks: - Psychiatric disorders (psychosis, depression, mania without known history, activation of previous psychiatric disorders) - Increase in susceptibility and severity of infections - Metabolism disorders - Growth inhibition in paediatric population - Cushing like Symptoms Important potential risks: - Use in pregnancy Missing information: - Use in lactating mothers	First version
2.0		No changes were made in regards to safety concerns.	Update sections following Day 70 RMS Assessment report and Day 100 CMSs comments: - Part I: Product Overview - Part II: Safety Specification - Part VI.2: Elements for a Public Summary

[i] Bell, G. (1991). Steroid-induced psychiatric disorders. Nordic Journal of Psychiatry, 45(6), 437-441.
[ii] C. T. Deshmukh, Minimizing side effects of systemic corticosteroids in children, Indian Journal of Dermatology, Venereology and Leprology, Vol. 73, Num. 4, 2007, pp. 218-221