VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Rheumatoid arthritis (RA):
Rheumatoid arthritis (RA) is a long-term disease in which the joints of the body become inflamed, causing pain, swelling and stiffness. RA typically affects the small joints of the hands and of the feet, and usually both sides equally and symmetrically, although any synovial joint (a joint lined with synovial tissue) can be affected. It is a systemic disease and so can affect the whole body, including the heart, lungs and the eyes.

The prevalence and incidence increase with age and peaks at about age 70 then declines, with around twice as many women as men developing RA. In addition the prevalence of RA is generally lower in developing countries.

Juvenile idiopathic arthritis (JIA):
Juvenile idiopathic arthritis (JIA) is a type of arthritis that causes persistent joint swelling, pain and limitation of movement in children under the age of 16. At its worst, JIA causes slow growth, joint contractures (shortening of the joint), eye problems and permanent disability. A high proportion of children develop destructive joint disease, often requiring early joint replacement. JIA is a relatively rare disease, with an estimated prevalence between 0.07 and 4.01 per 1,000 children.

Osteoarthritis and post-traumatic arthritis:
Osteoarthritis is a clinical syndrome of joint paint accompanied by varying degrees of functional limitation and reduced quality of life. It is the most common form of arthritis and one of the leading causes of pain and disability worldwide. Knees, hips and small joints are most commonly affected. Osteoarthritis is not caused by ageing and does not necessarily deteriorate.

Other inflammatory conditions (tendinitis, bursitis, synovitis, epicondylitis):
Soft tissue inflammatory conditions, such as tendonitis (inflammation of a tendon), bursitis (inflammation of one or more bursae (small sacs) of synovial fluid in the body) and synovitis (inflammation of the synovial membrane), commonly affect the shoulder, knee, elbow, hip or heel and produce pain, tenderness and restricted joint movement. Inflammation occurs most commonly due to overuse, but can be due to bacterial infections or related to a generalised rheumatic arthritis condition.

VI.2.2 Summary of treatment benefits

LEDOLAN is a medicinal product containing triamcinolone hexacetonide as the active ingredient. Triamcinolone hexacetonide has proved to be useful for the treatment of acutely inflamed joints in adults and juvenile forms of rheumatoid arthritis which were not controlled by systemic anti-inflammatory therapy.

The anti-inflammatory strength of triamcinolone on a milligram by milligram comparison is approximately five times that of hydrocortisone. The mechanism of action of LEDOLAN is based on the well-known anti-inflammatory and immunosuppressive effects of the pharmacological class of corticosteroids.

The product is formulated as a suspension for injection and should be administered via intraarticular, periarticular and intrasynovial routes (injection into the joint or surrounding tissue). The product must not be used for intravenous, intraocular, epidural or intrathecal use. The active substance triamcinolone hexacetonide is a synthetic glucocorticoid with very good anti-inflammatory effects.

LEDOLAN may also be used in children aged 3 – 12 years with Juvenile Idiopathic Arthritis. In this condition most paediatric rheumatologists routinely use intra-articular triamcinolone

hexacetonide in children down to 1 year of age and its use is very well established in clinical practice.

VI.2.3 Unknowns relating to treatment benefits

The safety profile for Ledolan is well established; currently no missing information related to treatment is identified.

VI.2.4 Summary of safety concerns

The adverse events listed in the SPC of Ledolan (triamcinolone hexacetonide) 20mg/ml suspension for injection are in accordance with the most recently approved Product Information of the reference product (and additional local reference product, Trigon Depot (triamcinolone acetonide) 40mg/ml, as requested by the Spanish regulatory authorities) .

Like other medicinal products, also Ledolan may produce skin disorders, allergic or hypersensitivity reactions caused by the active substance or by the excipients, especially by benzyl alcohol and sorbitol.

Triamcinolone hexacetonide shows only very low mineralocorticoid activity, and side effects on electrolyte balance are not clinically important. Patients with known acute psychosis are excluded from Ledolan treatment.

An additional safety issue is derived from the potential of the substance to interact with other drugs. Interactions may occur at the level of pharmacokinetics (e.g. enzyme inducers like rifampicin).

The only evidence of some relationship between dosage and reported adverse events concerns the smaller joints. Here, the risk of the development of a skin or subcutaneous atrophy appears to be higher, especially if strict intra-articular needle placement cannot be ascertained or too large a volume in relation to joint size is injected.

Important identified risks

Risk	What is known	Preventability
Active tuberculosis	Glucocorticoids inhibit and suppress the immune response. Aggravation of existing tuberculosis and reactivation of quiescent cases of this infection are classic consequences of glucocorticoid therapy.	Obtain a full medical history from the patient and in high risk cases, possible chest X-rays or blood test to determine previous exposure to TB.
Herpes simplex keratitis	Glucocorticoids inhibit and	Obtaining a full medical history

	suppress the immune response. The use of glucocorticoids in patients with bacterial keratitis increases their risk and predisposes them to ulcerative keratitis.	from the patient and in high risk cases an eye examination. Treat underlying infection prior to commencing treatment with a glucocorticoid.
Acute Psychoses	Glucocorticoids can affect and interact with other medications and may aggravate existing psychiatric symptoms.	Obtaining a full medical history from the patient and avoid treatment in patients with known psychosis conditions.
Systemic mycoses and parasitoses (strongyloid infections)	Glucocorticoids inhibit and suppress the immune response. Fungal and yeast infections can be precipitated or aggravated by glucocorticoid therapy.	Obtain a full medical history; treat underlying infections prior to commencing treatment.
Anaphylaxis and anaphylaxis-type reactions	Allergic and anaphylactic reactions to glucocorticoids have been reported, even though they have immunosuppressant effects.	Obtain medical history to identify patients with previous allergy or known hypersensitivity to this product.
Joint destruction caused by repeated intra-articular injections in long term use	Repeated injections may damage the joint. Severe joint destruction with necrosis of bone may occur if repeated intra-articular (in the joint) injections are given over a long period of time.	Monitor joint function and limit injections frequency.
Growth suppression in children	Corticosteroids are known to limit the growth of children by inhibiting human growth hormone.	If children are treated, limit the duration of the treatment and monitor for growth complications
Adrenocortical suppression	This product contains a potent glucocorticoid and so should be used with caution in patients suffering from the following conditions: Cushing's syndrome and hypothyroidism.	In order to minimise side effect it is recommended in using the lowest effective dose for the minimum period, and by administering the daily requirement, whenever possible, as a single morning dose on alternate days. Frequent patient review is required to titrate the dose appropriately against disease activity.
Osteoporosis and spontaneous fractures	The use of glucocorticoids is associated with reduced bone mineral density, bone loss, osteoporosis and fractures. Several mechanisms underlie the effects on bone. The effects on calcium are: (1) increased excretion of calcium into the bowel and inhibition of its absorption; (2) inhibition of tubular reabsorption of calcium in the kidney; (3) increased mobilisation of calcium from the skeleton. Other effects include: (1) a catabolic effect on protein metabolism,	Obtain a full medical history and monitor for signs of osteoporosis and adjust treatment accordingly.

	causing a reduction in the bone matrix; (2) altered vitamin D metabolism, with reduced vitamin D metabolites; (3) dose-dependent reduction of serum osteocalcin, a bone matrix protein.	
Peptic ulcers	The mechanism of harm that glucocorticoids do to the stomach is not clear. The symptoms of an existing peptic ulcer may be masked. Reports suggest people with hepatic cirrhosis or nephritic syndromes are particularly at risk.	Patients taking long term treatment should be closely monitored for peptic ulcers which can bleed and perforate without producing pain.
Increased intracranial pressure with papilloedema	Long term glucocorticoid treatment can result in papilloedema and increased intracranial pressure (the syndrome of pseudomotor cerebri or so-called 'benign intracranial hypertension), particularly in children. The symptoms can simulate those of an intracranial tumour.	Patients taking large doses of glucocorticoids, who complain of headache or blurred vision, particularly after a reduction in dosage, should be given an ophthalmoscopic examination.
Decreased carbohydrate intolerance and latent diabetes mellitus	All glucocorticoids increase gluconeogenesis. Glucocorticoid treatment of known diabetics normally leads to deregulation, but this can be compensated for by adjusting the dose of insulin. The turnover of glucose is increased, more being metabolised to fat and blood glucose concentrations is increased by 10-20%. Glucose tolerance and sensitivity to insulin are reduced, but provided pancreatic islet function is normal, carbohydrate metabolism will not be noticeably altered.	Obtain a full medical history and inform patient of possible need for adjustment to their treatment.

Important potential risks

Risk	What is known
Medication error	This formulation is intended for intraarticular, periarticular and intrasynovial use, and must not be used for intravenous, intraocular, epidural or intrathecal use.

*Meylers Side Effects of Drugs, 15th Edition. JK Aronson

Missing information

None

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.

The Summary of Product Characteristics and the Package leaflet can be found in the competent authority's webpage.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable as this is the first RMP for LEDOLAN.

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

Major changes to the Risk Management Plan over time

Version no.	Date	Safety concerns	Comment
1.0	April 2015	New RMP	Marketing Authorisation Application
2.0	November		Changes according to accessors comments.