RISK MANAGEMENT PLAN FOR JAYEMPI 10 MG/ML ORAL SUSPENSION

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Date for EU-RMP: 05-Jan-2024 Version 1.1

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LIST OF ABBREVIATIONS

6-MP	6-mercaptopurine
ATC	Anatomical Therapeutic Chemical (Classification)
CD	Crohn's disease
CMV	Cytomegalovirus
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
GMPS	Guanosine monophosphate synthetase
IBD	Inflammatory bowel disease
Ig	Immunoglobulin
INN	International Nonproprietary Name
ITPase	Inosine triphosphate pyrophosphatase
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
MPA	Mycophenolic acid
MOG	Myelin oligodendrocyte glycoprotein
NHS UKMi	National Health Service United Kingdom Medicines Information
NK	Natural killer
PAM	Post authorisation measure
PCV	Pneumococcal conjugate vaccine
PPSV	Pneumococcal polysaccharide vaccine
PSUR	Periodic safety update report
RA	Rheumatoid arthritis
RMP	Risk management plan
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TGN	Thioguanine nucleotide
TNF	Tumour necrosis factor
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis
QPPV	Qualified Person for Pharmacovigilance

Note: The terms 'trial' and 'study' may be used interchangeably throughout.

Table 1 Date and Version of the Risk Management Plan Parts / Modules when Last (Updated and) Submitted

RMP PART/MODULE	Version number when last submitted / or Not Applicable	Date Last Updated for Submission
PART II SAFETY SPECIFICATION		
Module SI Epidemiology of the indication(s) and target population(s)	1.0	30 Jun 2020
Module SII Non-clinical part of the safety specification	1.0	30 Jun 2020
Module SIII Clinical trial exposure	1.0	30 Jun 2020
Module SIV Populations not studied in clinical trials	1.0	30 Jun 2020
Module SV Post-authorisation experience	1.0	30 Jun 2020
Module SVI Additional European Union (EU) requirements for the safety specification	1.0	30 Jun 2020
Module SVII Identified and potential risks	1.1	05 Jan 2024
Module SVIII Summary of the safety concerns	1.0	29 Jan 2021
PART III PHARMACOVIGILANCE PLAN	1.1	05 Jan 2024
PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES	1.0	30 Jun 2020
PART V RISK MINIMISATION MEASURES	1.1	05 Jan 2024
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	1.1	05 Jan 2024
PART VII ANNEXES		
ANNEX 1 EudraVigilance Interface	1.0	29 Jan 2021
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	1.0	29 Jan 2021
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	1.0	29 Jan 2021
ANNEX 4 Specific adverse drug reaction follow-up forms	1.0	29 Jan 2021
ANNEX 5 Protocols for proposed and ongoing studies in RMP part IV	1.0	29 Jan 2021
ANNEX 6 Details of proposed additional risk minimisation activities (if applicable)	1.0	29 Jan 2021
ANNEX 7 Other supporting data (including referenced material)	1.0	29 Jan 2021
ANNEX 8 Summary of changes to the risk management plan over time	1.1	05 Jan 2024

Overview of European Union (EU)-Risk Management Plan (RMP) versions:

RMP version to be assessed as part of this application:

RMP version number: 1.1

Data lock point for this RMP: 05 Jan 2024

Date of final sign-off: 05 January 2024

Rationale for submitting an updated RMP:

Removal of the post-authorisation measure related to the annual monitoring of medication error reports specifically due to "conversion of patients from tablet to liquid formulation and two dosing syringes". This post-authorisation measure was considered fulfilled based on the assessment report for the Post-Authorisation Measure MEA/001.1.

Summary of significant changes in this RMP:

Part III, Part V and Part VI updated to remove reference to the Post-Authorisation Measure – annual monitoring of medication error reports.

Details of the currently approved RMP:

Version number: **1.0**

Approved with procedure: **EMEA/H/C/005055/0000**

Date of Approval: **21-Jun-2021**

Name of EU Qualified Person for Pharmacovigilance (QPPV):

QPPV Name:	Alexander Leigh
QPPV Signature:	
QPPV Oversight Declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder (MAH)'s / applicant's QPPV. The electronic signature is available on file.

PART I PRODUCT OVERVIEW

Table 2 Product Overview

Active Substance(s) (INN or common name):	Azathioprine
Pharmacotherapeutic group(s) (ATC code[s]):	Other immunosuppressants (L04A X01)
Marketing Authorisation Holder or Applicant:	Nova Laboratories Ireland Limited
Medicinal products to which this RMP refers:	Azathioprine Nova Laboratories, 10 mg/mL oral suspension
Invented name(s) in the European Economic Area (EEA):	Jayempi
Marketing authorisation procedure:	Centralised
Brief description of product including:	
Chemical class:	Azathioprine, an imidazole derivative of 6-mercaptopurine (6-MP), which acts as an immunosuppressant antimetabolite
Summary of mode of action	Azathioprine is rapidly broken down *in vivo* into 6-MP and 1-methyl-4-nitro-5-thioimidazole. 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Irrespective of whether it is given directly or is derived *in vivo* from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Azathioprine has an effect on both immunological reaction and tumour growth. Its major role has been as an agent for suppressing the immune response. The

	precise mechanism by which this effect is achieved is not known. However, the following mechanisms of action have been suggested: • The action of the released 6-MP as a purine antimetabolite • The possible blockage of -SH groups by alkylation • The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of immunocompetent cells (B- and T-lymphocytes) • The damage of deoxyribonucleic acid through incorporation of purine thioanalogues.
Important information about its composition	The solution contains sodium benzoate (E211)
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA:	
Current:	Jayempi is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogeneic kidney, liver, heart, lung or pancreas transplants. Azathioprine is indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression). Jayempi is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and / or procedures which influence the immune response. Jayempi is indicated in patients who are intolerant to glucocorticosteroids or if the therapeutic response is inadequate despite treatment with high doses of

	glucocorticosteroids, in the following diseases: • severe active rheumatoid arthritis (chronic polyarthritis) that cannot be kept under control by less toxic agents (disease-modifying anti-rheumatic – medicinal products - DMARDs) • autoimmune hepatitis • systemic lupus erythematosus • dermatomyositis • polyarteritis nodosa • pemphigus vulgaris and bullous pemphigoid • Behçet's disease • refractory autoimmune haemolytic anaemia, caused by warm immunoglobulin (Ig) G antibodies • chronic refractory idiopathic thrombocytopenic purpura Jayempi is used for the treatment of moderately severe to severe forms of chronic inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis) in patients in whom glucocorticosteroid therapy is necessary, but where glucocorticosteroids are not tolerated, or in whom the disease is untreatable with other common means of first choice. It is also indicated in relapsing multiple sclerosis, if an immunomodulatory therapy is indicated but beta interferon therapy is not possible, or a stable course has been achieved with previous treatment with azathioprine. Jayempi is indicated for the treatment of generalised myasthenia gravis. Depending on the severity of the disease, Jayempi

	should be given in combination with glucocorticoids because of slow onset of action at the beginning of treatment and the glucocorticoid dose should be gradually reduced after several months of treatment.
Proposed:	Not applicable
Dosage in the EEA:	
Current:	For oral use *Transplantation* Depending on the immunosuppressive regime selected, a dosage of up to 5 mg/kg body weight/day may be given on the first day of therapy. The maintenance dose can range from 1 to 4 mg/kg body weight/day and must be adjusted according to the clinical requirements and haematological tolerance. Azathioprine therapy should be maintained indefinitely, even if only low doses are necessary, because of the risk of graft rejection. *Multiple sclerosis-adults only* The usual dose for the treatment of relapsing forms of multiple sclerosis is between 2 and 3 mg/kg body weight/day. Treatment duration of more than 1 year may be required until manifestation of the effect, and at least 2 years may be needed until the disease is actually under control. *Myasthenia gravis* The recommended dose for the treatment of myasthenia gravis is 2 mg/kg to 3 mg/kg body weight/day. Treatment success usually occurs 2 to 6 months after the start of treatment at the earliest. Depending on the severity of the disease, Jayempi should be given in combination with glucocorticosteroids at the

	start of treatment because of the slow onset of the effect. The dose of glucocorticosteroids can be gradually reduced over several months. Treatment with Jayempi should be continued for at least 2 to 3 years. *Chronic active autoimmune hepatitis* The initial dosage is usually between 1.0 and 1.5 mg/kg body weight/day, and the maintenance dosage is up to 2 mg/kg body weight/day. *Dosage in other conditions* In general, the starting dosage is 1 to 3 mg/kg body weight/day and should be adjusted according to the clinical response (which may not be evident for weeks or months) and haematological tolerance. When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 to 6 months, consideration should be given to withdrawing the medicinal product. The maintenance dosage required may range from less than 1 mg/kg/body weight/day to 3 mg/kg/body weight/day depending on the clinical condition being treated and the individual patient response, including haematological tolerance. However, in patients with IBD treatment duration of at least 12 months should be considered, whereby a response to treatment may only be recognisable clinically after 3 to 4 months.
Proposed:	Not applicable

Pharmaceutical form(s) and strength(s):	
Current:	Oral suspension One mL of suspension contains 10 mg azathioprine
Proposed:	Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: 6-MP = 6-mercaptopurine; ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; IBD = inflammatory bowel disease; INN = International Nonproprietary Name; RMP = risk management plan; TPMT = thiopurine methyltransferase.

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATIONS

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

Indication: The indication and the safety profile of Jayempi 10 mg/mL oral suspension remains the same as that of the reference product; therefore, the most frequent uses are presented for discussion of epidemiology of the target population.

Inhibition of Transplant Rejection

Incidence: The annual number of organ transplantations varies between countries. Based on the statistics published by the joint Global Observatory on Donation and Transplantation (http://www.transplant-observatory.org), in 2018 there were 27,738 kidney transplants, 10,481 liver transplants, 2,801 heart transplants, 2,183 lung transplants, 801 pancreas transplants and 43 small bowel transplants performed in Europe.

Prevalence: The estimated total population of the EU is 513 million (Eurostat news release, Jul 2019). The number of transplantations in the EU may be roughly estimated to be 86 transplants per million EU population per year. These patients represent the target population that would potentially need to receive immunosuppressive medication such as azathioprine.

The exact number of organ transplant patients requiring immunosuppressive therapy is unknown. It is estimated that there are hundreds of thousands of patients in the EU that need immunosuppressive therapy after an organ transplant.

Demographics of the Population in the Proposed Indication: All age groups, increasing incidence with increasing age. Gender specificity is based on the underlying disease; exact statistics are not available.

Risk Factors: Transplantation is a life-saving surgery. The supply of donor organs is significantly lower than demand for them. Immunosuppression is an essential treatment to maintain a functioning transplanted allogeneic organ.

Main Existing Treatment Options: Allogeneic transplantation requires immunosuppression to facilitate successful organ transplant acceptance by the recipient and many different forms of treatment have been developed.

This immunosuppression is facilitated by corticosteroids such as prednisone or methylprednisolone alone or combined with immunosuppressants such as azathioprine, mycophenolate mofetil or sirolimus, or by administration of calcineurine inhibitors (cyclosporine, tacrolimus) or other agents (biologicals).

Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity: Most centres report more than 70% survival after 5 years for heart, lung, liver and kidney transplantations.

Important Co-morbidities: Opportunistic infections, co-morbidities linked to the underlying disease that led to the organ transplant.

Severe Rheumatoid Arthritis

Incidence: Severe RA represents less than 50% of all newly diagnosed cases of RA (Scott et al., 2010). It is estimated that 5 to 50 cases of RA per 100,000 population are diagnosed annually.

Prevalence: Overall, approximately 0.5 to 1% of adults in industrialised nations are affected by RA (Scott et al., 2010).

Demographics of the Population in the Proposed Indication: Prevalence of RA rises with increasing age and is more common in women >65 years of age.

Risk Factors: RA increases morbidity and mortality in the population and often leads to premature death.

Main Existing Treatment Options: Disease-modifying anti-rheumatic drugs (DMARDs) represent the first line of RA treatment strategy. DMARDs are given as monotherapy or in a combination with other DMARDs, such as methotrexate, leflunomide, hydroxychloroquine and sulfasalazine. Immunosuppressant methotrexate is usually the first drug choice.

Biological agents represent the newest treatment option for patients with RA who are not adequately responsive to DMARD preparations. Tumour necrosis factor (TNF)-α inhibitors (infliximab, adalimumab) or rituximab may be used. Biological preparations are usually combined with DMARD administration.

As with any other autoimmune diseases, administration of immunosuppressives in combination with glucocorticoids is also considered a treatment option. To ease some symptoms of RA, analgesics or nonsteroidal anti-inflammatory drugs may also be used.

Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity: RA has been shown to increase the risk of death caused by heart-related (cardiovascular) diseases (Liao 2017).

Important Co-morbidities: Cardiovascular disease and osteoporosis.

Ulcerative Colitis and Crohn's Disease

Incidence: Inflammation of the gut affects about 37 to 246 patients per 100,000 population (for UC) and 26 to 199 patients per 100,000 population (for CD) (Loftus 2004).

Prevalence: The annual rate of new diagnosis ranges between 5.6 patients for CD to 10.4 patients for UC per 100,000 EU population aged 15 to 64 years (Shivananda et al., 1996).

Demographics of the Population in the Proposed Indication: Slightly more common in females than males.

Risk Factors: Both of the chronic IBDs lead to increased associated morbidity and premature mortality in severe disease.

Main Existing Treatment Options: Corticosteroids are the mainstay of conventional therapy; therapeutic alternatives in steroid-refractory severe disease are cyclosporine, tacrolimus or biologicals.

Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity: 17.1 per 1,000 person-years (Card et al., 2003).

Important Co-morbidities: None.

Systemic Lupus Erythematosus

Incidence: SLE represents between 2.2 to 5 new diagnoses per 100,000 European inhabitants per year.

Prevalence: The overall number of patients suffering from SLE per 100,000 EU population is estimated as 20.5 to 71 patients (Danchenko et al., 2006).

Demographics of the Population in the Proposed Indication:

Risk Factors: SLE increases the risk of life-threatening diseases, in particular of those with involvement of the vascular pathophysiology (cerebrovascular, cardiovascular).

Main Existing Treatment Options: The European League Against Rheumatism released recommendations for the treatment of SLE (Bertsias et al., 2008). In patients with SLE without major organ manifestations, glucocorticoids and antimalarial agents may be beneficial. Nonsteroidal anti-inflammatory drugs may be used for short periods in patients at low risk for complication from these drugs.

Immunosuppressive agent use (e.g., azathioprine, mycophenolate mofetil and methotrexate) is considered in refractory cases or when steroids cannot be reduced to levels for long-term use (Mosca et al., 2010).

In patients with neuropsychiatric manifestations that may have an inflammatory aetiology, immunosuppressive agents may be considered.

Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity: Linked to clinical manifestation and co-morbidity.

Important Co-morbidities: Cardiovascular disease and osteoporosis.

Autoimmune Hepatitis

Incidence: Autoimmune hepatitis affects about 10.7 patients per 100,000 population (Werner et al., 2008).

Prevalence: As above.

Demographics of the Population in the Proposed Indication: Autoimmune hepatitis affects patients of all ages and gender across all geographic regions but is more common in females than males (Lowe and John, 2018). Results from a large Danish nationwide population-based study demonstrated the peak age of incidence at more than 60 years for both men and women (Grønbæk et al., 2014).

Risk Factors: Untreated severe cases can lead to cirrhosis and hepatic failure. Many patients have existing cirrhosis at the time of diagnosis.

Main Existing Treatment Options: Corticosteroids, either alone or in combination with azathioprine.

Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity: Undiagnosed disease leads to significant morbidity and mortality; however, timely initiation of treatment leads to a favourable outcome in the majority of cases. For patients who present with a severe acute hepatitis, overall mortality is high (19% to 45%; Lowe and John, 2018).

Important Co-morbidities: None.

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

Key Safety Findings from Non-clinical Studies and Relevance to Human Usage:

The marketing authorisation applicant has not conducted its own non-clinical development programme for Jayempi. This section is, therefore, not applicable.

MODULE SIII CLINICAL TRIAL EXPOSURE

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

Current available exposure specific to Jayempi 10 mg/mL oral suspension is based on a single-centre, single-dose, open-label, randomised, two-period crossover study to assess the bioequivalence of an oral azathioprine suspension 10 mg/mL (Jayempi™) versus oral azathioprine tablet 50 mg (Imurek®, Aspen Pharma Trading Limited, Dublin, Ireland) in at least 30 healthy adult subjects under fasting conditions.

Exposure based on duration, dose, age group and gender (by indication), age group and gender (by indication and product) and ethnic origin are presented in Table 3, Table 4, Table 5, Table 6 and Table 7, respectively.

Clinical Trial Exposure by Duration of Exposure

Table 3 Extent of Exposure by Duration (by Indication)

Healthy Adult Volunteers		
Duration of exposure	**Persons**	**Person time**
1 day (single-dose)	30	59 days
Total person time for indication	30	59 days

Clinical Trial Exposure by Dose

Table 4 Extent of Exposure by Dose (by Indication)

Healthy Adult Volunteers		
Dose of exposure	**Persons**	**Person time**
50 mg	30	59 days

Clinical Trial Exposure by Age Group and Gender

Table 5 Extent of Exposure by Age Group and Gender (by Indication)

Healthy Adult Volunteers				
Age group	**Persons**		**Person time**	
	Male	**Female**	**Male**	**Female**
19 – 52 years	19	11	37 days	22 days

Table 6 Extent of Exposure by Age Group and Gender (by Product)

Azathioprine 10 mg/mL oral suspension				
Age group	**Persons**		**Person time**	
	Male	**Female**	**Male**	**Female**
19 - 52 years	18	11	18 days	11 days
Azathioprine 50 mg tablet				
Age group	**Persons**		**Person time**	
	Male	**Female**	**Male**	**Female**
19 – 52 years	19	11	19 days	11 days

Clinical Trial Exposure by Ethnic Origin

Table 7 Extent of Exposure by Racial / Ethnic Origin (by Indication)

Healthy Adult Volunteers		
	Persons	**Person time**
Caucasian	27	53 days
Asian	1	2 days
Black or African American	2	4 days

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Not applicable.

MODULE SV POST-AUTHORISATION EXPERIENCE

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

SV.1 Post-authorisation Exposure

Not applicable.

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

Potential for Misuse for Illegal Purposes

Not applicable.

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 05 Jan 2024

RMP version number when this module was last updated: 1.1

Justification of new safety concern "Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes" with a submission of this RMP in comparison with the reference medicinal product Imurek:

Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes, and interaction with live and inactivated vaccines, are both considered important potential risks.

Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes is a new potential risk for Jayempi 10 mg/mL oral suspension in comparison with the reference medicinal product Imurek. As the possibility of conversion of patients from pre-approved tablet formulation to liquid formulation cannot be excluded, due to the ease of the administration especially in paediatric patients and patients with dysphagia, this has been considered as an additional potential risk for Jayempi 10 mg/mL oral suspension. Although considered bioequivalent as per the bioequivalence study results, the risk of a potential medication error in the calculation of dose and its administration cannot be excluded due to the use of two syringes for dispersion of the Jayempi 10 mg/mL oral suspension before administration.

Also, the potential for medication error due to use of two syringes may increase the risk of overdose if used incorrectly.

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:

Below are the 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 either the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU member state where the product is authorised) or which do not require any additional pharmacovigilance or additional risk minimisation activities:

- Myelosuppression (bone marrow suppression)

- Opportunistic infections (immunosuppression/infections)
- Neoplasm (carcinogenicity and mutagenicity)
- Interaction with live and inactivated vaccines
- Hypersensitivity to active substance azathioprine, to 6-mercaptopurine or to any other excipient;
- Potential interaction with xanthine oxidase inhibitor (allopurinol, febuxostat), neuromuscular blocking agent, ribavirin, other myelosuppressive agents;
- Drug exposure during pregnancy, breastfeeding/lactation and teratogenicity;
- Use in patients with hepatic impairment, renal impairment and pancreatitis;
- Macrophage activation syndrome in IBD patients;
- Progressive multifocal leukoencephalopathy;
- Genetic variation (thiopurine methyltransferase [TPMT], NUDT15, and Lesch-Nyhan syndrome).
- Rhabdomyolysis, inosine triphosphatase deficiency, and hepatotoxicity are well-documented potential risks for other generic azathioprine products; therefore, these risks are also included in this section.
- Use in the elderly is listed as missing information in the RMPs of other generic azathioprine products; therefore, this has been included as missing information that can be monitored by routine pharmacovigilance activities.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks:

Not Applicable.

Important Potential Risk 1: Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes

Risk-benefit impact: Low, as the Jayempi 10 mg/mL oral suspension SmPC specifies the method of administration, which will keep this risk under control.

With approved oral tablet formulations available on the market there is a chance of conversion of patients from oral tablet to oral suspension, especially in the paediatric population and patients with dysphagia. The Jayempi 10 mg/mL oral suspension is accompanied by two syringes for dispersing the suspension before administration. With conversion there is the possibility of an impact on dose, although Jayempi 10 mg/mL oral suspension is considered bioequivalent and, therefore, interchangeable as per the data available from the bioequivalence study. There is also a risk of potential medication error with use of two syringes for dose calculation and administration. This can also increase the risk of overdose.

Jayempi 10 mg/mL oral suspension provides clear instructions in Section 4.2 (Posology and method of administration) to avoid the potential for medication error. As Jayempi 10 mg/mL oral suspension will only be available on prescription, there will always be oversight by the prescribing physician/specialist.

As per section 4.4 of the Jayempi 10 mg/mL oral suspension SmPC, physicians/health care personnel should recommend patients/carers for weekly haematological monitoring during first 8 weeks of treatment and thereafter monthly or at least at intervals of no longer than 3 months.

Risks will be managed via routine pharmacovigilance activities and Nova Laboratories Ireland Ltd. will use a follow-up questionnaire form for medication error to follow-up medication error cases due to conversion from tablets to liquid formulation. In addition as per required additional pharmacovigilance activities medication error reports specifically due to "conversion of patients from tablet to liquid formulation and two dosing syringes" will be monitored annually and submitted as post authorisation measure (PAM) outside the context of azathioprine PSUR.

Important Potential Risk 2: Drug exposure during pregnancy and breastfeeding

Risk-benefit impact: Low, as it is available on prescription only and prescribing physicians and dispensing pharmacists will be made aware about contraindication of the product during lactation and potential effects of Jayempi 10 mg/mL oral suspension on pregnancy outcome and the potential of toxic effects on the foetus and infants via maternal and paternal exposure to Jayempi 10 mg/mL oral suspension via the Jayempi SmPC.

Azathioprine comes under the category D-evidence of human risk of the Food and Drug Administration. Although there are some concerns regarding azathioprine use, with foetal abnormalities shown in animals, most practitioners consider this medication as a safe alternative based on its long record of use in transplant recipients (Al-Otaibi et al., 2019). In a national cross sectional survey of Canadian rheumatologists regarding management of inflammatory arthritis in pregnancy, respondents agreed that azathioprine (76%) can be continued throughout pregnancy and was safe during all pregnancies. This is in alignment with European League Against Rheumatism points and British Society for Rheumatology, British Health Professionals in Rheumatology guidelines for the continuation of azathioprine, hydroxychloroquine and sulfasalazine during pregnancy. (De Vera et al., 2019).

Azathioprine is commonly used as steroid-sparing agent in the management of myasthenia gravis. Although several studies have reported increased rates of prematurity, intrauterine growth retardation and low birth weight, there is no increased risk of foetal malformations in infants born to mothers exposed to azathioprine during pregnancy as per few authors. This is likely related to the absence of enzymes in the foetal liver, which converts azathioprine to its active metabolite. Currently, azathioprine is considered as non-steroidal drug of choice in the management of pregnant myasthenic women in Europe given in a dose of 2 to 3 mg/kg body weight. It is still considered as a risky drug in the United States based on case reports, which suggested that infants exposed to azathioprine *in utero* have an increased risk of infections,

anaemia, leukopenia and thrombocytopenia. The author recommended that, although azathioprine could be a drug of choice during pregnancy for patients who are intolerant to steroids, breastfeeding should be avoided in patients taking azathioprine as it is excreted in breast milk, or administration during breastfeeding should be undertaken only after discussing the possible risk with the mother (Bansal et al., 2018).

A retrospective observational study compared paternal exposure of mycophenolic acid (MPA) and non-MPA (receiving azathioprine N = 8 and not receiving azathioprine N = 5) for kidney-transplanted patients. In non-MPA groups there were two reports of miscarriage and one report of Down's syndrome, although it was not specified if these patients received azathioprine or not. However, none of the 21 children in the non-MPA group and none in the MPA group showed physical malformations, and birth weights were also comparable between groups (Lopez-Lopez et al., 2018).

Studies in women with IBD, SLE or transplantation taking doses of azathioprine up to 200 mg daily for immunosuppression have found either low or unmeasurable levels of the active metabolite in milk and infant serum. Some evidence indicates a lack of adverse effects on the health and development of infants exposed to azathioprine during breastfeeding up to 3.5 years of age but long-term follow-up for effects such as carcinogenesis have not been performed. Mothers with decreased activity of the enzyme that detoxifies azathioprine metabolites may transmit higher levels of drug to their infants in breast milk. Cases of mild, asymptomatic neutropenia have been reported and so it might be desirable to monitor exclusively breastfed infants with a complete blood count with differential and liver function tests, if azathioprine is used during lactation, although some authors consider that monitoring is unnecessary. Avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant in breast milk. Most experts consider breastfeeding during azathioprine to be acceptable, however, there has been evidence of low blood counts and infections in the infants whose mothers were exposed to azathioprine during pregnancy (US National Library of Medicine, 2006).

It is known that considerable amounts of azathioprine and its metabolites pass through the placenta and amniotic sac, and are thereby transferred from the mother to the foetus. Malformations due to azathioprine occurred in animal experiments. In animal studies, azathioprine was teratogenic and embryotoxic. There are conflicting findings on the teratogenic potential of azathioprine in humans. Azathioprine must only be used during pregnancy after a careful benefit/risk analysis.

Blood count changes (leukopenia and/or thrombocytopenia) have been reported in a number of neonates whose mothers received azathioprine during pregnancy. Extra care in haematological monitoring of the mother is advised during pregnancy. Temporary impairment of the immune response was detected in neonates from intrauterine exposure to a combination of azathioprine with prednisone. There have been reports of intrauterine growth retardation, premature births and low birth weights vis-à-vis azathioprine, in particular in combination with corticosteroids. Moreover, data is available on spontaneous abortions after both maternal and paternal exposure. Chromosomal abnormalities, which disappear with

time, have been demonstrated in lymphocytes of the offspring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with azathioprine (Jayempi SmPC).

The active metabolite of azathioprine, 6-mercaptopurine, has been identified in the colostrum and breast milk of women receiving azathioprine treatment (Jayempi SmPC). Furthermore, azathioprine is proven to be mutagenic in a number of *in vitro* and *in vivo* genotoxicity assays (Jayempi SmPC). Sections 4.3, 4.6 and 5.3 of the Jayempi 10 mg/mL oral suspension SmPC provide clear instruction regarding this risk. This risk will be managed via routine pharmacovigilance activities and drug exposure during pregnancy and breastfeeding cases will be documented in the PSUR.

Important Missing Information:

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

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

Risks related to a specific formulation or route of administration:

With the formulation as oral suspension, the conversion of patients from an earlier approved tablet formulation of azathioprine with oral suspension is possible. Although Jayempi 10 mg/mL oral suspension is considered bioequivalent and, therefore, interchangeable as per the data available from the bioequivalence study, the risk of a potential medication error with use of two syringes for dose calculation and administration leading to incorrect dose or overdose cannot be excluded. Please refer to Table 8 below for further information.

Risks relating to a specific target population:

Not applicable.

Risks associated with switch to non-prescription status:

Not applicable.

Table 8 Details of Important Identified and Potential Risks

Important Identified Risks: Not applicable	
Important Potential Risk #1	
Risk: Potential medication errors - Conversion of patients from tablet to liquid formulation and two dosing syringe	
Potential mechanisms	Not applicable.
Evidence source and strength of evidence:	National Health Service (NHS) United Kingdom Medicines Information (UKMi ; https://www.ukmi.nhs.uk/) NHS UK Alternatives to liquid pharmaceutical specials, for patients unable to take solid oral dosage forms
Characterisation of the risk	With an approved oral tablet formulation available on the market, there is a chance of conversion of patients from oral tablet to liquid formulation, especially in the paediatric population and patients with dysphagia. The Jayempi 10 mg/mL oral suspension is accompanied by two syringes for dispersing the suspension before administration. With conversion there is a possibility of an impact on dose, although Jayempi 10 mg/mL oral suspension is considered bioequivalent and, therefore, interchangeable as per the data available from the bioequivalence study. There is also a risk of potential medication error with use of two syringes for dose calculation and administration. This can also increase the risk of overdose. With this, there is an increased chance of other risks of Jayempi 10 mg/mL oral suspension i.e. myelosuppression and opportunistic infections.
Risk factors or risk groups	Paediatric and elderly age groups, and patients with dysphagia who were prescribed with the tablet formulation.
Preventability	Supervision by the prescribing physician / specialist as a 'prescription only use' medicinal product will help to keep this risk of medication error under control. Referring to Section 4.2 (Posology and method of administration) of the Jayempi 10 mg/mL oral suspension SmPC before starting on Jayempi 10 mg/mL oral suspension, where the dosing of azathioprine with the help of two syringes is explained in detail, will also help to keep the risk of medication error under control.
Impact on the risk-benefit balance of the product	Low, as the Jayempi 10 mg/mL oral suspension SmPC specifies the method of administration in detail, which will keep this risk under control.
Public health impact	Not applicable.
Important Potential Risk #2	
Risk: Drug exposure during pregnancy and breastfeeding	
Potential mechanisms	Azathioprine is an antineoplastic immunomodulating, immunosuppressive antimetabolite. Azathioprine is an inactive 6-MP, which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to TGNs for immunosuppression. TGNs and other metabolites (e.g. 6-MP ribonucleotides) inhibit de novo purine synthesis and purine nucleotide interconversions. The TGNs are also incorporated into nucleic acids and this contributes to the immunosuppressive effects of the drug. Azathioprine also inhibits many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of cells in the immune response i.e. B- and T-lymphocytes. Azathioprine is rapidly metabolised in vivo by

	glutathione S-transferase into the metabolites 6-MP and 1-methyl-4-nitro-5-thioimidazole. The metabolite, 6-MP, passes cell membranes rapidly and is extensively metabolised in numerous multistep metabolic processes into active and inactive metabolites without any enzyme being predominantly active. Azathioprine can induce mutations in human cells and can interfere with DNA repair mechanisms; these drugs could potentially influence the risk of several types of cancer. From another perspective, cancer cells could also be considered vulnerable to its action because azathioprine disrupts cell division. Azathioprine is known to be mutagenic; mutation in somatic cells could lead to cancer.
Evidence source and strength of evidence:	Jayempi 10 mg/mL oral suspension SmPC Al-Otaibi et al 2019 De Vera et al 2019 Bansal et al 2018 Lopez-Lopez et al 2018 US National Library of Medicine, Azathioprine
Characterisation of the risk	Azathioprine comes under the Food and Drug Administration category D-evidence of human risk. It is known that considerable amounts of azathioprine and its metabolites pass through the placenta and amniotic sac, and are thereby transferred from the mother to the foetus. Malformations occurred in animal experiments due to azathioprine. In animal studies azathioprine was teratogenic and embryotoxic. There are conflicting findings on the teratogenic potential of azathioprine in humans. Azathioprine must only be used during pregnancy after a careful benefit/risk analysis. Blood count changes (leukopenia and/or thrombocytopenia) have been reported in a number of neonates whose mothers received azathioprine during pregnancy. Extra care in haematological monitoring of the mother is advised during pregnancy. Temporary impairment of the immune response was detected in neonates from intrauterine exposure to a combination of azathioprine with prednisone. There have been reports of intrauterine growth retardation, premature births and low birth weights vis-à-vis azathioprine, in particular in combination with corticosteroids. Moreover, data is available on spontaneous abortions after both maternal and paternal exposure. Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes of the offspring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with azathioprine. The active metabolite of azathioprine, 6-MP, has been identified in the colostrum and breast milk of women receiving azathioprine treatment. Azathioprine was mutagenic in a number of in vitro and in vivo genotoxicity assays.
Risk factors or risk groups	Pregnant and/or breastfeeding females, females of reproductive age group and foetuses or infants exposed to Jayempi 10 mg/mL oral suspension via maternal or paternal exposure. Patients using intrauterine devices (IUD; coil or T-shaped ‘copper coil’) without additional contraceptive measure, as this contraceptive measure can fail under azathioprine therapy.

Preventability	Both male and female patients of reproductive age should use contraceptive methods while using azathioprine. Men should not father children during and up to 6 months after the end of treatment. This also applies to patients with limited fertility due to chronic uraemia, as fertility generally returns to normal after a transplant. To use additional contraception for the patients using IUD, coil or T-shaped copper coil. Azathioprine should be contraindicated while breastfeeding. If treatment with azathioprine is unavoidable, breastfeeding should be discontinued.
Impact on the risk-benefit balance of the product	Low, as it is available on prescription only and prescribing physicians and dispensing pharmacists will be made aware about the contraindication of the product during lactation and potential effects of Jayempi 10 mg/mL oral suspension on pregnancy outcomes and the potential of toxic effects on the foetus and infants via maternal and paternal exposure to Jayempi 10 mg/mL oral suspension via the Jayempi SmPC.
Public health impact	Low.

Abbreviations: 6-MP = 6-mercaptopurine; SmPC = Summary of Product Characteristics

SVII.3.2 Presentation of the Missing Information

Not applicable.

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 29 Jan 2021

RMP version number when this module was last updated: 1.0

A summary of safety concerns is presented in Table 9.

Table 9 Summary of Safety Concerns

Important identified risks	Not applicable
Important potential risks	1. Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes 2. Drug exposure during pregnancy and breastfeeding
Missing information	Not applicable

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 05 Jan 2024

RMP version number when this module was last updated: 1.1

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires for Pregnancy / Lactation:

Nova Laboratories Ireland Ltd. will use a standard pregnancy follow-up form/questionnaire to follow-up on cases of pregnancy / lactation.

Other Forms of Routine Pharmacovigilance Activities:

Nova Laboratories Ireland Ltd. will use a follow-up questionnaire form for medication error to follow-up medication error cases due to conversion from tablets to liquid formulation.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Required additional pharmacovigilance activity is presented in Table 10.

Table 10 Ongoing and Planned Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due dates**
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				
None				

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 30 Jun 2020

RMP version number when this module was last updated: 1.0

Not applicable.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 05 Jan 2024

RMP version number when this module was last updated: 1.1

V.1 Routine Risk Minimisation Measures

The safety information in the proposed product information is aligned to the reference medicinal product and also on an evaluation of the literature reported studies of azathioprine in IBD, Crohn's disease (CD) and ulcerative colitis (UC). A description of routine risk minimisation measures by safety concern is presented in Table 11.

Table 11 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Not applicable	
Important Potential Risks	
Potential Risk # 1	
Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes	**Routine risk communication:** Please refer to the following sections of the Jayempi 10 mg/mL oral suspension SmPC: Sections 4.2 (Posology and method of administration) and 4.9 (Overdose). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** As per Section 4.2 of the Jayempi 10 mg/mL oral suspension SmPC, physicians/health care personnel should recommend patients/carers on appropriate dosing of Jayempi as per the specific indication. As per section 4.4 of the Jayempi 10 mg/mL oral suspension SmPC, physicians/health care personnel should recommend patients/carers for weekly haematological monitoring during first 8 weeks of treatment and thereafter monthly or at least at intervals of no longer than 3 months. In the event of azathioprine overdose, Section 4.9 of the Jayempi 10 mg/mL oral suspension SmPC notes that active measures (such as usage of activated charcoal) will probably only be effective if they are carried out within 60 minutes of ingestion. **Other routine risk minimisation measures beyond the product information:** Prescription-only medicinal product.

Potential Risk # 2	
Drug Exposure during Pregnancy and Breastfeeding	**Routine risk communication:** The safety information in the proposed product information is aligned to the reference medicinal product. Please refer to the following Sections of the Jayempi 10 mg/mL oral suspension SmPC: Sections 4.3 (contraindications), 4.6 (Fertility, pregnancy and lactation), section 5.3 (preclinical safety data). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Per section 4.3 of Jayempi 10 mg/mL oral suspension SmPC, Jayempi is contraindicated during lactation. Per Section 4.6 of Jayempi 10 mg/mL oral suspension SmPC, both male and female patients of reproductive age should use contraceptive methods while using azathioprine. Men should not father children during and up to 6 months after the end of treatment. This also applies to patients with limited fertility due to chronic uraemia, as fertility generally returns to normal after a transplant. Additional contraceptive methods should be recommended for females using intrauterine devices (coil or T-shaped copper coil), with the evidence that it can fail under azathioprine therapy. Extra care in haematological monitoring of the mother is advised during pregnancy. If treatment is unavoidable with azathioprine during breastfeeding, then breastfeeding should be discontinued. Per Section 5.3 of Jayempi 10 mg/mL oral suspension SmPC, Jayempi was embryotoxic and mutagenic in pre-clinical studies and hence must only be used during pregnancy after a careful benefit/risk analysis. **Other routine risk minimisation measures beyond the product information:** Prescription only medicinal product.
Important Missing Information	
Not applicable.	

Abbreviations: SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimisation Measure

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

Removal of Additional Risk Minimisation Activities

Not applicable.

V.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures in presented in Table 12.

Table 12 Summary of Risk Minimisation Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Not applicable.		
Important Potential Risks		
Potential Risk # 1 Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes	Routine risk minimisation measures: Please refer to the following Sections of the Jayempi 10 mg/mL oral suspension SmPC: Sections 4.2 (Posology and method of administration) and 4.9 (Overdose). The Patient Information Leaflet emphasises colour coding of both the dosing syringes and different sizes of these syringes will have less chance of medication error due to use of two syringes. Additional risk minimisation measures: Not applicable.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: All reports of medication errors will be monitored closely and presented in the PSUR. Additional pharmacovigilance activities: None.
Potential Risk # 2 Drug exposure during pregnancy and breastfeeding	Routine risk minimisation measures: Please refer to the following Sections of the Jayempi 10 mg/mL oral suspension SmPC: Sections 4.3 (contraindications), 4.6 (Fertility, pregnancy and lactation), and 5.3 (preclinical safety data). Additional risk minimisation measures: Not applicable.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: All the reports of drug exposure during pregnancy & its outcome and drug exposure during breastfeeding will be monitored closely and presented in PSUR. Additional pharmacovigilance activities: None.
Important Missing Information: Not applicable		

Abbreviations: PSUR = periodic safety update report; SmPC = Summary of Product Characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Jayempi 10 mg/mL oral suspension contains the active ingredient azathioprine

Active substance(s): Azathioprine

Product(s) concerned: Jayempi 10 mg/mL oral suspension

MAH / MAA name: Nova Laboratories Ireland Ltd.

Data lock point for this module: 05 Jan 2024

RMP version number when this module was last updated: 1.1

Summary of the Risk Management Plan for Jayempi 10 mg/mL Oral Suspension (Azathioprine)

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

Jayempi 10 mg/mL oral suspension's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Jayempi 10 mg/mL oral suspension should be used.

This summary of the RMP for Jayempi 10 mg/mL oral suspension should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Jayempi 10 mg/mL oral suspension's RMP.

I. The Medicine and What it is Used For

Jayempi is authorised for the conditions outlined in Table 2. (See SmPC for full indication). It contains azathioprine as the active substance and it is given orally (by mouth).

In general, the starting dosage is 1 to 3 mg/kg body weight/day and the maintenance dose required may range from less than 1 mg/kg/body weight/day to 3 mg/kg/body weight/day depending on the clinical condition being treated; the dose is adjusted by the treating physician according to the patient's clinical response.

For other specific medical conditions, the following doses should be given:

Up to 5 mg/kg body weight/day may be given on the first day of therapy following organ transplantation in adults and children; the maintenance dose can range from 1 to 4 mg/kg body weight/day and is adjusted according to the clinical requirements;

Between 2 and 3 mg/kg body weight/day for the treatment of chronic autoimmune neuromuscular diseases (relapsing forms of multiple sclerosis and myasthenia gravis);

Between 1.0 and 1.5 mg/kg body weight/day for the treatment of chronic liver disease (chronic active autoimmune hepatitis); the maintenance dosage is up to 2 mg/kg body weight/day.

Further information about the evaluation of Jayempi 10 mg/mL oral suspension's benefits can be found in Jayempi 10 mg/mL oral suspension's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <*link to the EPAR summary landing page*>.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Jayempi 10 mg/mL oral suspension, together with measures to minimise such risks and the proposed studies for learning more about Jayempi 10 mg/mL oral suspension's risks, are outlined below.

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

- 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 will be collected continuously and regularly analysed, reported and included in periodic safety update reports (PSURs) as applicable, so that action(s) can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

The important information that affects the safe use of Jayempi, which is not yet available, is listed under 'missing information'.

II.A List of Important Risks and Missing Information

Important risks of Jayempi 10 mg/mL oral suspension are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken.

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 Jayempi 10 mg/mL oral suspension. 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).

A list of important identified/potential risks/missing information is provided in Table 13.

Table 13 List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important Identified Risks	Not applicable
Important Potential Risks	1 Potential medication errors - conversion of patients from tablet to liquid formulation and two dosing syringes 2 Drug exposure during pregnancy and breastfeeding
Missing Information	Not applicable

II.B Summary of Important Risks

A summary of important potential risks is provided in Table 14.

Table 14 Summary of Important Potential Risks

Important potential risk: Potential medication errors - Conversion of patients from tablet to liquid formulation and two dosing syringes	
Evidence for Linking the Risk to the Medicine	National Health Service (NHS) United Kingdom Medicines Information (UKMi ; https://www.ukmi.nhs.uk/) NHS UK Alternatives to liquid pharmaceutical specials, for patients unable to take solid oral dosage forms
Risk Factors and Risk Groups	Paediatric and elderly age groups, and patients with dysphagia who were prescribed with the tablet formulation.
Risk Minimisation Measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). All reports of medication errors will be monitored closely.
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: None
Important potential risk: Drug exposure during pregnancy and breastfeeding	
Evidence for Linking the Risk to the Medicine	Evidence for this risk comes from published literature.

Risk Factors and Risk Groups	Pregnant and/or breastfeeding females, females of reproductive age group and foetus or infants exposed to Jayempi via maternal or paternal exposure. Patients using intrauterine devices (coil or T-shaped 'copper coil') without additional contraceptive measure, as this contraceptive measure can fail under azathioprine therapy.
Risk Minimisation Measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures. Additional risk minimisation measures: Not applicable.
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: None.

Abbreviation: PSUR = periodic safety update report.

IIC Post-Authorisation Development Plan

IIC.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies that are conditions for the approval of the marketing authorisation.

II.C.2 Other Studies in Post-Authorisation Development Plan

None.

PART VII ANNEXES

Annex 4: Specific Adverse Event Follow-Up Forms

Pregnancy Report Form v3.0, 23 January 2020

Pregnancy Outcome Form v3.0, 06 August 2020

Medication Error Form v1.0, 16 December 2020

Pregnancy

ICON Project Number: 3245-0008 and 3245-0009

Send to ICON PV AND SAFETY SERVICES E-MAIL:
ICON-Safety-CentralReceipt@iconplc.com (ROW)

Part 1: This form is to be used as an INITIAL notification that a pregnancy has occurred.

Date Reporter notified of Pregnancy: _____ -_____ -_____
DD MMM YYYY

Date of this Report: _____ -_____ -_____
DD MMM YYYY

Patient Information

Year of Birth: _____
YYYY

☐ Female (Maternal Exposure) ☐ Male (Paternal Exposure)

Pregnancy Information

Method of Birth Control (if applicable):_____

Pregnancy Initially Diagnosed by (check all that apply): ☐ Home Urine test ☐ Outpatient department Urine test ☐ Serum test

Start date of last period: _____ -_____ -_____ Date Pregnancy Confirmed: _____ -_____ -_____
DD MMM YYYY DD MMM YYYY

Anticipated due date: _____ -_____ -_____
DD MMM YYYY

Methodology for calculation: ultrasound ☐
Manual calculation method ☐
Other (specify)……

Prenatal tests completed:		
	☐ (MS) AFP __ -___ -_____ DD-MM-YYYY	☐ Amniocentesis __ -___ -_____ DD-MM-YYYY
	☐ Ultrasound __ -___-_____ DD-MM-YYYY	☐ Other (specify) __ -___ -_____ DD-MM-YYYY

Was there evidence of a birth defect or genetic disorder from prenatal test? ☐ No ☐ Yes

If Yes, indicate which tests(s) revealed evidence of birth defects. (Add details to additional information section)	☐ (MS) AFP ☐ Amniocentesis _
	☐ Ultrasound ☐ Other (specify) _

Medical History

Obstetric History:
Number of Pregnancies: _____ Number of Births:_____ Number of Miscarriages:_____
Number of Terminations:_____

Medical History Relevant to Pregnancy (including conception and fertility history, pregnancy risk factors, smoking, alcohol, environmental or chemical hazards, etc.):

Drugs Taken During Pregnancy

Product(s)	Total Daily Dose (mg)	Duration of Therapy (DD-MMM-YYYY)		Indication
		Started	Stopped	

ICON Project Number: 3245-0008 and 3245-0009					
Send to ICON PV AND SAFETY SERVICES E-MAIL: **ICON-Safety-CentralReceipt@iconplc.com (ROW)**					
Part 1: This form is to be used as an INITIAL notification that a pregnancy has occurred.					
Additional Information					
Attending Obstetrician	**Name & Address / Contact Details:** **Name:** _____ **Address:** _____ _____ **Telephone Number:** _____ **Fax Number:** _____				
Reporter	**Pregnancy Reported By:** **Print Name:** _____ **Signature:** _____ **Date:** _____-_____-_____ DD MMM \YYYY				

IMPORTANT: Please **do not** send additional documents with this Pregnancy form, but add any relevant information to the Pregnancy form itself.

NOTE: Please ensure **Personal Information** that could **potentially identify the patient is not included in any document** that is sent to **ICON** as per **ICH GCP Principles 2.11, EU General Data Protection Regulation (GDPR)** and other **applicable laws and legislations.**

Pregnancy Follow-up

ICON Project Number: 3245-0008/9

Send to ICON PV AND SAFETY SERVICES E-MAIL:
ICON-Safety-CentralReceipt@iconplc.com (ROW)

Part II: This form is to be used as a FOLLOW-UP notification regarding the outcome of the pregnancy.

Patient Information

Date of Report: _____-_____-_____ (DD MMM YYYY)

Year of Birth _____ (YYYY)

☐ Female (Maternal Exposure) ☐ Male (Paternal Exposure) ☐ No further information available (Please provide details):

Course of Pregnancy

List any exposure(s) during the course of the pregnancy:

Smoking: _____ cig./day

Alcohol: _____ glasses/day

Substance Abuse: ☐ No ☐ Yes, Specify: _____

Environmental or Chemical Hazards: ☐ No ☐ Yes, Specify:

List any significant illness(es) during the course of the pregnancy:

Pregnancy Outcome

Date of Delivery: _____-_____-_____ (DD MM YYYY)

Live Newborn: ☐ Yes ☐ No | Details: _____

Mode of Delivery: ☐ Vaginal ☐ Assisted Vaginal ☐ Caesarian

Malformations/anomalies diagnosed in foetus or at birth: ☐ Yes ☐ No

Dysmaturity: ☐ Yes ☐ No

Placenta Normal: ☐ Yes ☐ No

Condition of Newborn

Gender: ☐ Female ☐ Male

Weight: _____ kg / _____ Lbs

Length: _____ cm / _____ inches

Head Circumference: _____ cm / _____ inches

APGAR Score: 1 minute: _____ 5 minutes: _____

Termination/Abortion Information

Reason for Termination: _____

Results of Physical Examination (Gender, external anomalies) and Pathology _____

_____

_____

Gestation Age at Termination: _____(days/weeks)

Pregnancy Follow-up

ICON Project Number: 3245-0008/9

Send to ICON PV AND SAFETY SERVICES E-MAIL:
ICON-Safety-CentralReceipt@iconplc.com (ROW)

Part II: This form is to be used as a FOLLOW-UP notification regarding the outcome of the pregnancy.

Concomitant Drugs/Treatment Taken During Pregnancy

Drug Name/Treatment	Total Daily Dose (mg)	Duration of Therapy (DD-MMM-YYYY)		Indication
		Started	Stopped	

Additional Information

(Such as, relevant medical history (including paternal history), Neonatal illness, hospitalization, drug therapies)

Attending Obstetrician

Name & Address / Contact Details:

Name: _____

Address: _____

_____

Telephone Number: _____ **Fax Number:** _____

Reporter

Pregnancy Reported By:

Print Name: _____

Signature: _____ **Date:** _____ -_____-_____
DD MMM YYYY

IMPORTANT: Please **do not** send additional documents with this pregnancy follow-up form, but add any relevant information to the pregnancy follow-up form itself.

NOTE: Please ensure **Personal Information** that could **potentially identify the patient is not included in any document** that is sent to **ICON** as per **ICH GCP Principles 2.11, EU General Data Protection Regulation (GDPR)** and other **applicable laws and legislations.**

Medication Error Form: Jayempi/ Azathioprine Oral Suspension

MAH: Nova Laboratories

Send to ICON PV AND SAFETY SERVICES E-MAIL:
ICON-Safety-CentralReceipt@iconplc.com (ROW)

Part 1: This form is to be used as a follow-up notification for medication errors that has been occurred while using Jayempi

Date Reporter notified of Medication Error : _____ -_____ -_____
DD MMM YYYY

Date of this Report: _____ -_____ -_____
DD MMM YYYY

Patient Information

Gender (Male/Female):

Age (years) / Year of Birth:

Weight (Kg):

Height (cm)

Jayempi Therapy Details

Indication:

Start date: Stop Date:

Dose: Duration: Frequency:

Route of administration:

Batch Number: Lot No: Expiry Date:

Medication Error Details

Date of Medication error occurrence: Time of medication error occurrence:

Error detected by:

Error made by :

Confirmation by HCP:

Any previous instances of medication error and it's details:

Type of error:

□ Prescribing error □ Dispensing error □ Administration error □ Syringe issue

If Administration error, Choose the reason below:

□ Monitoring error
□ Inappropriate schedule of drug administration
□ Drug administration by inappropriate route
□ Inappropriate dose of drug administered
□ Wrong technique in drug administration process/ Inappropriate drug extraction with syringe
□ Syringe broken/ Syringe leak/ Syringe issue
□ Syringe connection issue/ Device connection issue
□ Syringe marking confusion/Device confusion issue
□ Other ,please specify

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□ Medication error/ syringe issue led to Overdose

If yes,
□ Action taken with Jayempi due to overdose
□ Treatment given for overdose

□ In case of leakage, was anyone exposed to the product ---------

□ Any associated AE/SAE's
If yes,

Event	Seriousness	Onset date	Stop date	Outcome	Treatment	Action taken with Jayempi	Causality with Jayempi

□ Clinical course of the patient with regard to overdose/associated AE/SAE's

□ If syringe issue, was replacement of syringes requested

□ What action was taken with Jayempi dosing due to medication error

Lab data (results of any regular hematological monitoring due to conversion from tablet to oral suspension and any additional hematological monitoring done due to medication error occurred):

Additional relevant information for the medication error occurred

Reporter

Medication Error reported By:

Print Name: _____

Signature: _____ **Date:** _____-_____-_____
DD MMM \YYYY

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