22 April 2021
EMA/303143/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jayempi

International non-proprietary name: azathioprine

Procedure No. EMEA/H/C/005055/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Quality

BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CRS	Chemical Reference Substance (official standard)
DAD	Diode Array Detection
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
MCC	Microcrystalline cellulose
6-MP	6-mercoaptopurine
Ph. Eur.	European Pharmacopoeia
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
PET	Preservative Efficacy Test

Clinical/Non-Clinical

6-MeTIMP	6-methylthioinosine monophosphate
6-MP	6-Mercaptopurine
6-MPN	6-Mercaptopurine Nucleotides
6-TG	6-Thioguanine
6-TGN	6-Thioguanine Nucleotides
8-OHMP	8-Hydroxy-6-Mercaptopurine
ACE	Angiotensin Converting Enzyme
ADME	Absorption, Distribution, Metabolism, Excretion
ANOVA	Analysis of variance
AUC	Area Under the Curve
BMI	Body mass index
CD	Cluster of Differentiation
CLp	Plasma Clearance
Cmax	Maximal Concentration
CNS	Central nervous system

CV	Coefficient of variation
DCP	Decentralised procedure
DMARDs	Disease-modifying anti-rheumatic drugs
DNA	Deoxyribonucleic Acid
EC	European Commission
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMPS	Guanosine monophosphate synthetase
HPLC	High Performance Liquid Chromatography
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
HSDB	Hazardous Substances Data Bank
i.p.	Intraperitoneal
i.v.	Intravenous
IARC	International Agency for Research on Cancer
IBD	Inflammatory Bowel Disease
IMP	Investigational medicinal product
ISR	Incurred Sample Reanalysis
ITPase	Inosine triphosphate pyrophosphatase
IV	Intravenous
kg	Kilogram
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
MNACI	1-methyl-4-nitro-5-(N-acetyl-S-cysteinyl) imidazole
MNGI	1-methyl-4-nitro-5-(S-glutathionyl)-imidazole
MNTI	1-methyl-4-nitro-5-thioimidazole
MRP	Mutual recognition procedure
MS	Mass spectrometer
MTX	Methotrexate
N, N'-MNIC	N,N'-[5-(1-Methyl-4-Nitro)Imidazolyl]Cystine
NUDT15	Nudix Hydrolase 15
p.o.	Per Os (L: By Mouth)
PD	Pharmacodynamics
PDCO	Paediatric Committee
PK	Pharmacokinetic
RBC	Red Blood Cells
s.c.	Subcutaneous
SCE	Sister Chromatid Exchange
SmPC	Summary of Product Characteristics
STD	Standard
TEAE	Treatment-emergent adverse event
TGNs	Thioguanine nucleotides
TPMT	Thiopurine Methyl Transferase

TUA	Thiouric Acid
UHPLC	Ultra high performance liquid chromatography
UK	United Kingdom
VDss	Steady-state volume of distribution
XO	Xanthine Oxidase

* This is a general list of abbreviations. not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nova Laboratories Ireland Limited submitted on 21 November 2019 an application for Marketing authorisation to the European Medicines Agency (EMA) for Jayempi, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Jayempi is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic 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 drugs – DMARDs)
- auto-immune hepatitis
- systemic lupus erythematosus
- dermatomyositis
- polyarteritis nodosa
- pemphigus vulgaris and bullous pemphigoid
- Behçet's disease
- refractory auto-immune haemolytic anaemia, caused by warm IgG 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.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Imurek 50 mg film-coated tablets instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Imurek 50mg film-coated tablets
- Marketing authorisation holder: Aspen Pharma Trading Limited
- Date of authorisation: 30-11-2004
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 6101735.00.00

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form:Imurek 50mg film-coated tablets
- Marketing authorisation holder: Aspen Pharma Trading Limited
- Date of authorisation: 30-11-2004
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 3101735.00.00

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Imurek 50mg film-coated tablets
- Marketing authorisation holder: Aspen Pharma Trading Limited
- Date of authorisation: 30-11-2004
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 3101735.00.00
- Bioavailability study number(s): INV691

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg Co-Rapporteur: N/A

CHMP Peer reviewer: N/A

The application was received by the EMA on	21 November 2019
The procedure started on	2 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	06 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	18 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	26 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 February 2021 18 February 2021

The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the 2nd CHMP consolidated List of Outstanding Issues on	23 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	07 April 2021
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	15 April 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jayempi on	22 April 2021

2. Scientific discussion

2.1. Introduction

Azathioprine has been in clinical use as an immunosuppressant for more than 50 years. Azathioprine is an inactive 6-mercaptopurine derivative (6-MP), which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for immunosuppression. It belongs to the Pharmacotherapeutic group: Antineoplastic and immunomodulating active substances; Immunosuppressive agents – Other immunosuppressive agents. ATC code: L04AX01.

TGNs and other metabolites (e.g. 6-methylmercaptopurine 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. Other potential mechanisms of azathioprine include the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of cells involved in the immune response (B and T lymphocytes).

With respect to oral therapy, only a tablet form of azathioprine in a limited number of strengths is available. This inflexibility in dosing poses a challenge to accurate dosing and titrating to the optimum dose, especially in children. An age appropriate azathioprine formulation has been identified by the EMA Paediatric Working Party/Paediatric Committee as a paediatric need in different areas such as gastroenterology (EMA/PDCO/552359/2015), immunology (EMEA/381922/2006) and rheumatology (EMEA/CHMP/234105/2005). Nova Laboratories Ireland Limited has therefore developed an oral liquid formulation of azathioprine for use in adults and children.

One bioequivalence study (INV691) was conducted to support this application using the reference product is Imurek 50 mg film-coated tablets marketed by Aspen Pharma Trading Limited and first authorised in the community on 30 November 2004 and sourced from Germany.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral suspension containing 10mg/mL of azathioprine as active substance.

Other ingredients are: sodium benzoate (E211), sucralose (E955), banana flavour, citric acid monohydrate, microcrystalline cellulose and carmellose sodium, xanthan gum, and purified water.

The product is available in an amber type III glass bottle with tamper evident child-resistant closure (HDPE with expanded polyethylene liner) containing 200 mL of oral suspension.

Each pack contains one bottle, an HDPE bottle adaptor, a 3 mL polyethylene oral dosing syringe with red plunger (0.1 mL dose graduations) and a 12 mL polyethylene oral dosing syringe with white plunger (0.25 mL dose graduations), as described in section 6.5 of the SmPC.

2.2.2. Active substance

The chemical name of azathioprine is 6-[(1-Methyl-4-nitro-1*H*-imidazol-5-yl)sulfanyl]-7*H*-purine corresponding to the molecular formula $C_9H_7N_7O_2S$. It has a relative molecular mass of 277.26 g/mol and the following structure:

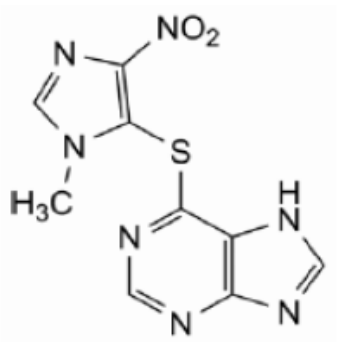


Figure 1: active substance structure

The active substance is a pale-yellow powder, practically insoluble in water and in ethanol (96 per cent), soluble in dilute solutions of alkali hydroxides, and sparingly soluble in dilute mineral acids.

No indication of hygroscopicity has been revealed in stability studies performed by the active substance manufacturer.

No polymorphism has ever been detected in azathioprine by the active substance manufacturer.

As there is a monograph of azathioprine in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for azathioprine which has been provided within the current Marketing Authorisation Application. The Certificate of Suitability confirms that the azathioprine is suitably controlled by the Ph. Eur. monograph (no. 0369).

Manufacture

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests as per Ph. Eur. Monograph 0369, namely: identification (Ph. Eur.), assay (Ph. Eur.), related substances (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), water content (KF), heavy metals (ICP-MS), and residue on ignition (Ph. Eur.). In addition, the manufacturer of the active substance controls ethanol (a residual solvent) by GC, in accordance with the current CEP. The finished product manufacturer (Nova Laboratories) applies the same specification for active substance testing with an additional test for particle size distribution (laser diffraction). All additional methods have been adequately validated and described according to ICH Q2 (R1).

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The maximum daily dose of azathioprine administered is ≤ 2 g/day. Therefore, the limit for any unspecified impurity of 0.10% as stated in the monograph meets the requirements of Ph. Eur. 2034. The limits specified for the impurities A and B and the total impurities are also according to the same monograph.

The finished product manufacturer performs a particle size test on receipt as a check to confirm the absence of large aggregates. The particle size of the azathioprine, as received, has been shown to be of a suitable particle size for an oral suspension and is supported by data obtained from the bioequivalence study. The particle size has been shown to be quite consistent during the manufacture and stability studies performed for the finished product. Since the particle size may influence the stability of the finished product and *in vivo* dissolution, the applicant was requested to tighten the upper particle size specification limit D(v,0.9) based on the batch data for this attribute, or otherwise justify the limitchosen for the active substance specification. The applicant submitted additional D(v,0.9) particle size data obtained from the active substance manufacturer and based on forty-four batches of active substance. The conclusion from the process capability charts is that the upper specification limit could be tightenedDetails of the analytical procedure used for the determination of the particle size distribution and its validation report have been provided.

The reference standards by the finished product manufacturer for testing the active substance are those required in the Ph Eur monograph for azathioprine 0369, namely EDQM CRS reference standards azathioprine, impurity A and G CRS. This is acceptable.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The active substance is stored in the delivery containers from receipt to manufacture of the finished product at Nova Laboratories, which are double polyethylene bags placed in either a fibre or a plastic drum. Reference is made to the CEP with confirmation that the container closure system used for the storage of the active substance is the same as that specified on the CEP and assessed by the EDQM. This is adequate.

Stability

The applicant refers to the data submitted to the EDQM, and therefore the re-test period of the substance is that specified on the CEP, that is 5 years if stored in double polyethylene bags placed in either a fibre or a plastic drum. No further information was submitted. This is adequate.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product, Jayempi 10 mg/mL oral suspension is a yellow viscous suspension. Its composition, per nominal 1 mL dose and per 200 mL bottle has been presented.

The product has been developed as a hybrid of Imurek 50mg tablet, based on the fact that it has a different pharmaceutical form and a different strength.

The suspension is filled into amber Type III glass bottles at a nominal fill of 200 mL, and closed with a tamper evident, child resistant, high density polyethylene (HDPE) screw cap. The liquid contact surface (wad) is expanded polyethylene.

The bottle and other components are packaged in a cardboard carton. In use, the screw cap is removed, a low-density polyethylene (LDPE) syringe adapter, for use with an oral dosing syringe, is inserted into the neck of the bottle and the original cap replaced. Graduated 3 mL and 12 mL dosing syringes are provided with each bottle. The medical devices have been CE-marked prior to submission of the dossier for the medicinal product.

The choice of the size of the syringes was discussed by the applicant to address a major objection raised during the review regarding the possible confusion with the inclusion of two syringes to choose from to measure the required dose and potential medication errors. The applicant has submitted a study report to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions throughout the entire dose ranges which simulate the use of the product. In addition, clear instructions have been included in the SmPC on how the doses are to be measured accurately with the syringes provided.

Azathioprine is a cytotoxic, imidazole derivative of 6-mercaptopurine (6-MP). It has been used as an immunosuppressant antimetabolite either alone or in combination with other agents for the prophylaxis of transplant rejection. It is also used to treat an array of autoimmune diseases, including rheumatoid arthritis. It is also an important therapy and steroid-sparing agent for inflammatory bowel disease (such as Crohn's disease and ulcerative colitis) and for multiple sclerosis.

For transplants, the initial dose in adults and children is up to 5 mg/kg and the usual maintenance dose is 1-4 mg/kg/day. In autoimmune conditions, the typical maintenance dose is 1-3 mg/kg/day. Doses are adjusted according to clinical response and haematological tolerance. Therefore, the daily dose of azathioprine can vary significantly, for example for children up to 9 years based on the 50th percentile weight (according to WHO growth data) doses are expected to be from 3.3. mg to 143.4 mg.

Therefore, the applicant claimed that the optimum mg/kg dosing for a child of any given age, results in a wide range of doses that can only be truly individualised and delivered accurately with an oral liquid formulation. Moreover, liquid preparations are considered as the formulation of choice for younger paediatric patients unable to swallow capsules or tablets. However, currently, in the EU, azathioprine is only available as 25mg, 50mg, 75mg and 100mg tablets.

There are some limitations associated with the active substance, being a BCS Class IV drug, highly insoluble in aqueous media and relatively unstable in alkaline conditions.

With these objectives and limitations in mind, a suspension formulation was selected for development. A liquid formulation, rather than a powder for reconstitution, was chosen in order to minimise handling operations (especially the potentially dusty powder handling operations) for a cytotoxic drug. Thus, the quality target product profile (QTPP) was to develop a palatable oral suspension formulation at a concentration of 10 mg/mL, in a pack size of 200 mL, which can facilitate dose adjustment, with a minimum shelf-life of 12 months, and intended for the treatment of a variety of conditions, particularly in children.

The applicant has identified the physico-chemical properties of the active substance that are clinically relevant, e.g. particle size and solubility. These properties have been adequately specified and controlled.

In fact, as indicated under the active substance section, the applicant was requested to justify the choice of the particle size specification and whether it should include particle size distribution instead of the one limit of D (v, 0.9) chosen, based on the possible effect of the particle size and its distribution on the dissolution, solubility and bioavailability, the processing during manufacture, the stability, uniformity of content and product appearance relevant to the suspension (ref. decision tree #3 of ICH Q6A quality guideline) and the potential for particle growth. Development data to support the discussion was also requested.

The particle size was also tested throughout stability and shows no significant change between the active substance and the finished product. Furthermore, there was no significant change in particle size at any storage condition for up to 24 months. The discussion presented by the applicant adequately justifies that by setting the limits at D(V,0.9) and D(V, 0.5) the particle size specification is considered appropriate for a BCS class IV molecule for controlling of the largest particles, coupled with a discriminatory dissolution test.

Regarding the viscosity of the formulation, the applicant has stated that the mixture provides adequate viscosity to the suspension to ensure that there is very minimal sedimentation of particles and quicker re-dispersion of sedimented particle upon shaking to allow accurate measurements and dosing.

Viscosity is a critical parameter for this proposed oral suspension and although some of the formulation studies submitted have included its measurement, a good discussion on this critical parameter was lacking at day 120 including an appropriate justification which is expected for the proposed release and stability specification for this parameter. In his responses, the applicant provided more detailed discussion on the choice of proposed viscosity specification for the finished product and tightened its limit. The in-use stability data shows that the viscosity of the formulation decreases slightly during the 12 weeks in-use period, however, homogeneous doses can be withdrawn as demonstrated by the homogeneity of suspension data.

The excipients included in the formulation are regularly used in these amounts in similar products. These include sodium benzoate (preservative), sucralose (sweetener), banana liquid flavour (flavouring agent), microcrystalline cellulose and carmellose sodium (suspending agent), xanthan gum (viscosity modifier), citric acid monohydrate (pH modifier) and water (diluent/vehicle). No novel excipients have been used in this proposed oral suspension.

The applicant has discussed the choice of excipients including their use in pharmaceutical suspensions for paediatric use and their effect on the acceptability of the final finished product to children with respect to thixotropic properties required by the suspension to deliver the correct dose as well as other aspects such as pH, microbiological attributes and physical and chemical stability.

Compendial excipients comply with the monograph in the current edition of the European Pharmacopoeia. The applicant has confirmed they will continue to comply with any monograph revision that may be issued in the future. The applicant confirmed that each excipient is qualified in-house to ensure full compliance to the relevant compendial monograph for the parameters which were not included in the CoAs submitted for the excipients. This is acceptable.

For xanthan gum the applicant has discussed some of the functional related characteristics listed in the Eur Ph monograph. A specific grade manufactured to be suitable for use in pharmaceutical preparations and which allows faster hydration upon contact with water is used. The particle size, viscosity and viscosity ratio of xanthan gum is controlled by the manufacturer to ensure that there is no significant variation in the rheological properties of the finished product. The applicant has updated the relevant sections of the dossier to include the specific grade of xanthan gum used.

For the microcrystalline cellulose and carmellose sodium (MCC) powdered mixture, the applicant has mentioned the control of the particle size of the excipient in order to aid suspension stability. The applicant has confirmed the grade employed. The particle size is controlled by the manufacturer to ensure that there is no significant difference in the physical properties of finished product. Viscosity is listed as a functionality related characteristic in the Ph. Eur. monograph (2050) for the microcrystalline cellulose and carmellose sodium (MCC) powdered mixture when used as a suspending agent. Therefore, the applicant has updated their specification to include this parameter.

Banana liquid flavour is added to mask the taste of the active substance and other components of the suspension, and aid patient acceptability. The specifications for this non compendial excipient have been listed. The flavour complies with Regulation (EC) N° 1334/2008 which is acceptable for this product which is an oral suspension.

None of the compendial excipients detailed above contain any material derived from human and animal origins and hence do not pose a Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathy (TSE) risk.

The quantities of the excipients were adequately discussed for the use in this oral suspension, except for the preservative, sodium benzoate, where more justification was required.

The applicant presented a study with a formulation without any preservative and varying concentrations of two different preservatives: sodium benzoate and domiphen bromide to justify that a preservative was required. To address this major objection, the applicant provided preservative efficacy data for the 18 months samples stored at 25°C/60% RH and 35°C/65% RH for three pilot scale batches. The Preservative Efficacy Test (PET) data after 18 months stability for all the batches met the specification criteria as defined in the Efficacy of Antimicrobial Preservation Test (Ph. Eur 5.1.3). The applicant stated that the inclusion of sodium benzoate at specific concentration is therefore required in the proposed azathioprine formulation to provide adequate antimicrobial protection during the shelf-life. However the azathioprine formulations with lower concentrations of sodium benzoate at different were all able to meet the acceptance criteria for the preservative efficacy test and therefore it was not justified that the concentration used in terms of efficacy and safety is the minimum concentration of preservative that gives the required level of efficacy throughout the intended shelf life of the product.

In his day 180 responses, the applicant presented further data to discuss and justify his initial choice of the concentration of sodium benzoate.

The applicant also carried out preservative efficacy testing on a 19-month-old batch of azathioprine suspension after 14-weeks of in-use stability testing. It also met the preservative efficacy test criteria demonstrating that the preservative, sodium benzoate, is effective through to the end of the proposed shelf life and in-use period.

This is acceptable and the major objections raised with respect to the preservative system and its efficacy are considered resolved.

During the review, the applicant was also requested to discuss in more detail the development of the finished product in line with the "Guideline on pharmaceutical development of medicines for paediatric use", for aspects such as safety of all the excipients and acceptability of the proposed product with respect to the palatability of the formulation. This was satisfactorily addressed, including a consideration of the safety aspect of the excipients in children as well as a reference to a study done to assess the palatability.

A discussion on the suitability of this formulation for use within the geriatric population was also requested. This was addressed as per the "draft CHMP Reflection paper on the pharmaceutical development of medicines for use in the older population (EMA/CHMP/QWP/292439/2017)".

At day 120, another major objection was raised because the applicant only provided an overview of the studies conducted for the formulation development, but the actual results from all these studies that support the conclusions reached were missing. The applicant has updated section 3.2.P.2.2 to include further data and discussion in response to the specific issues raised.

A discussion and rationale for the development of the dissolution method, its discriminatory nature and for the proposed specification limit and its clinical relevance was submitted following a major objection raised by the CHMP**.** The studies submitted by the applicant support the choice of the dissolution method.

The dissolution profiles of test product (Azathioprine 10 mg/mL oral suspension batch 1267f004 used in the bioequivalence study) at pH 1.3 (0.1M HCl), pH 4.5 (acetate buffer) and pH 6.8 (phosphate buffer), were provided.

With regards to the manufacturing process development, the applicant has outlined the order and steps required for the optimum manufacturing process to be attained. During developmental trials the critical steps have been identified. Three stability batches (pilot batches of 30L) manufactured by this process were stated to confirm the suitability of the process.

As indicated above, the primary packaging consists of an amber type III glass bottle with tamper evident child-resistant closure (HDPE with expanded polyethylene liner) containing 200 ml of oral suspension.

Each pack contains one bottle, an HDPE bottle adaptor and 2 polyethylene dosing syringes: a 3 mL oral dosing syringe (with 0.1 mL dose graduations) and a 12 mL oral dosing syringe (with 0.25 mL dose graduations). The material complies with Ph. Eur. and EC requirements for materials which are in contact with food (1935/2004). The bottle adaptor and the syringes have a CE mark. The relevant declaration of conformity has been submitted by the notified body for the syringes and adaptor. It includes the TSE declaration.

These syringes have been primarily selected based on the typical doses administered to children in the age range 2 to 9 years (who are most likely to prefer an oral liquid), ensuring a palatable volume and accuracy down to 1 mg increments. It is however accepted that Jayempi azathioprine 10 mg/mL oral suspension may also be beneficial in adolescents and adult patients, especially those with difficulty swallowing tablets (for example dysphagia in elderly patients or secondary to stroke). Based on reports, the mean maintenance dose in transplant patients is 1-2 mg/kg/day and in inflammatory disease is approximately 2-2.5 mg/kg/day, a typical 80 kg adult patient would need up to 20 mL of liquid, which is achievable with two uses of the 12 mL syringe.

At day 120 the applicant was requested to present the extractables and leaching studies conducted as compatibility studies of the formulation with the measuring devices. The applicant responded that a compatibility study of the formulation with the measuring device has not been performed as the

migration studies carried out by the supplier along with the low aqueous solubility of azathioprine and the transient nature of the contact between the finished product and the syringe, confirm the potential of extractables and leachables from the syringe into the finished product can be considered negligible. This is acceptable.

Both the measuring devices are CE marked and are compliant with the EU regulations for materials in contact with food. For both syringes, overall migration and specific migration studies have been performed by the supplier as described in European Commission regulation (EC) No 10/2011 (and amendments) relating to plastic materials and articles intended to come into contact with food including studies in aqueous solutions. The statement regarding compliance to GMO requirements is included in the declaration. A statement regarding TSE/BSE requirement for the Expanded Polyethylene Wad has also been provided.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process comprises a number of mixing of the excipients and homogenisation steps in sequential order, followed by pH adjustment, addition and dispersion of the active substance and filling. The process is considered to be a non-standard manufacturing process.

There are no process intermediates generated during this manufacturing process.

Adequate details have been given for the sequence of the process steps, as well as the speed and times for mixing and temperature at which this takes place.

The main critical steps and the IPCs have been identified.

Samples are taken during the filling process at the start, middle and end of filling. The typical length of a production run has been defined the applicant declared that the start of shelf life conforms to the NfG on the start of shelf-life of the finished product.

The applicant has submitted the process validation on three commercial scale batches.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), pH (Ph. Eur.), viscosity (Ph. Eur.), uniformity of mass of delivered doses (Ph. Eur.), azathioprine content (HPLC), identification of azathioprine (HPLC, DAD), impurities HPLC), sodium benzoate content (HPLC), identification of sodium benzoate (HPLC, DAD), homogeneity of suspension (HPLC), dissolution (Ph. Eur.), particle size (Ph. Eur.), TAMC, TYMC and *E. coli* (Ph. Eur.).

The discussion on the potential degradation products is acceptable and characterisation details of the degradation products have been provided. The applicant has justified the main degradation products of azathioprine 10 mg/mL oral suspension.

The maximum daily dose is taken as 400 mg. The qualification limit of 0.2% as per ICH Q3B has been applied for the specified impurities listed at release. The total impurity level has been justified. This is acceptable. The applicant was requested to submit additional information to support the qualification of the limits for some impurities which are higher than the qualification threshold stipulated by the Note for guidance on impurities in new drug products (CPMP/ICH/2738/99). The applicant submitted relevant literature in Module 4 at day 121 responses which supports the limits chosen for the end of shelf life for those impurities (see non-clinical section). This is acceptable.

During the review several questions on the proposed limits for different parameters were raised. All have been addressed and the revised specifications are acceptable.

In particular, as discussed under the pharmaceutical development section, during the review the applicant was requested to review proposed specification limit for particle size. Based on the data provided, the revised limits at D(V,0.9) and D (V, 0.5) are considered appropriate for a BCS class IV molecule for controlling of the largest particles, coupled with a discriminatory dissolution test.

For dissolution, the applicant initially proposed a dissolution specification without adequate justification, which resulted in a Major Objection. In their responses, they revised the dissolution test method with respect to the paddle speed and the specification limit. Based on the data provided, the applicant was requested to further tighten the dissolution limit. The applicant reviewed the dissolution data available and submitted a table showing that some of the batches, including the bio-batch, were non-compliant to the suggested tighter limit for individual values at the S1, showing the presence of some possible variability in the dissolution values which would not affect the product performance *in vivo*, due to the high solubility overall of the product, notwithstanding the active substance being of BCS Class IV. The CHMP acknowledges the potential for variability for the finished product dissolution, especially in view of the low rotation speed. The applicant has also shown that the test was discriminatory for a "bad" batch. In view of the review of dissolution data presented and the possible variability of the dissolution values shown which would affect neither the finished product performance nor the discriminatory power of the dissolution QC test, the proposal made by the applicant to keep the dissolution limit to the initially revised level, together with the commitment made to review "the specification post-approval, once a statistically appropriate number of active substance/finished product batches have been tested" is acceptable.

However, the applicant has committed to analyse the dissolution data from the first three commercial batches of Jayempi 10mg/ml oral suspension, and submit a variation to tighten the dissolution specification limit to the level requested by CHMP during the review if the data indicates that it is feasible (see recommendations section).

A risk analysis for elemental impurities following the recommendations of ICH Q3D Options 2b and 3 was performed. To support the predicted values of elemental impurities, 3 batches of azathioprine suspension were analysed for Class 1 and Class 2A elements. In addition, the levels of additional potential impurities were also measured and compared against the Option 3 limits as defined in ICH Q3D. The conclusion from the risk assessment and the batch analysis is that there are no Class 1 or Class 2A elemental impurities at a level above the control threshold (30% of the PDE) as defined in ICH 3QD, and that residues of additional potential impurities were also below control thresholds is acceptable. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A major objection on the lack of a risk evaluation concerning the potential presence of nitrosamine impurities in the product applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)" was raised during the procedure.

At day 121, the applicant provided a risk evaluation that included an appendix from the active substance manufacturer. The API manufacturer concluded that there is no risk of N-nitrosamine contamination of the API and that no confirmatory testing is required, however the risk evaluation provided did not consider all the currently known potential sources for N-nitrosamines formation. This was not acceptable.

The applicant submitted an updated risk evaluation in the D181 responses for both the active substance and finished product as requested, including aspects mentioned in the EMA guidance such as manufacturing equipment, cross contamination of manufacturing lines and storage of the finished product, as well as the possibility of the presence of nitrites and/or nitrosamines in the excipients using information gathered from the excipient/ raw materials and packaging suppliers as confirmation. The risk evaluation submitted determines the potential for nitrosamine contamination in accordance with EMA/189634/2019. The overall conclusion of the evaluation is that there is no risk for nitrosamine formation in Azathioprine Oral Suspension. Therefore Step 2 confirmatory Testing is not required.

The analytical methods used have been adequately described and non-compendial appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards for azathioprine and sodium benzoate has been presented. Azathioprine Chemical Reference Standard (CRS) sourced from EDQM is the primary reference standard. As Sodium Benzoate CRS from the EDQM is not available, the primary reference standard is defined as USP Sodium Benzoate RS.

Batch analysis results are provided for seven commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 4 commercial scale batches of finished product stored for up to 24 months under 5°C, 25°C/60% RH, 30°C/65% RH in upright position; 25°C/60% RH (inverted); and for up to 6 months at 40°C/75% RH (upright) according to the ICH guidelines. The batches of Jayempi are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, viscosity, azathioprine content, azathioprine related substances, sodium benzoate content, homogeneity of suspension, particle size, TAMC, TYMC, *E. Coli* and preservative efficacy.

Results show that the key parameters tested are within the proposed shelf life specification for all batches. No major differences were observed in data for batches stored at 25°C/60% RH upright and 25°C/60% RH inverted. There were no significant changes in parameters for product stored at 40°C/75% RH for 6 months, except fora couple of impurities, which both exceeded the shelf-life specification after about 4 months. In addition, the preservative system is demonstrated to be acceptable, with preservative efficacy data meeting the requirements of Ph. Eur. 5.1.3 and no total viable counts above the detectable limit.

A photo-stability study was also conducted on one batch. The packaging for Jayempi oral suspension consists of a 200 mL amber glass bottle as the primary container within a cardboard box secondary container. Samples were exposed to a minimum of 1.2 million lux hours and 2000-watt hours/m^2. Samples were tested for appearance, pH, viscosity, sodium benzoate content, azathioprine content and related substances. The data indicated that azathioprine is susceptible to photodegradation. However, storage in amber glass bottles offers sufficient protection against photo-degradation.

An in-use stability study was also conducted on one commercial 4-month-old and a 19-month-old batch for over 12 and 14 weeks, respectively. Bottles were stored at 15-25°C for the duration of both studies. On each day of sampling the bottle was removed from storage, the sample removed, then the bottle returned to 15-25°C storage. This allowed the withdrawal of product on up to 70 occasions from a single bottle of product. There was no detectable bioburden at the end of the study.

The test procedures used for the in-use stability studies were the same as those as defined in the specification. There was no loss of potency of azathioprine during the studies. There were no significant increases in any related substance over the duration of the studies. All analytical and microbiological parameters remained within specification. Microbiological contamination remained at very low levels and preservative efficacy met the requirements of Ph.Eur.5.1.3. Therefore, an in-use shelf life of 12 weeks when stored at no more than 25°C is supported.

Based on available stability data, the proposed shelf-life of 24 months when the product is stored unopened at a temperature of not more than 25°C, and an in-use shelf life of 12 weeks after first opening of the bottle, when stored at a temperature of not more than 25°C, as stated in the SmPC (section 6.3) are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product, Jayempi 10 mg/mL oral suspension, has been developed to facilitate administration of azathioprine to young children and patients who cannot swallow the existing tablet formulations.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

As discussed in the report a number of quality major objections were raised during the review. These pertained to the justification of the proposed QC dissolution method, the addition of particle size distribution to the finished product specification, the provision of a risk evaluation on the potential presence of nitrosamine impurities in the product, the suitability of the proposed syringes for the dosing of the product and instructions to the user and the missing data from the formulation development studies. All these have been resolved, with an outstanding recommendation for the applicant to evaluate the dissolution data from the first three commercial batches of the product and evaluate whether further tightening of the dissolution limit to the level requested by CHMP is feasible and submit a variation to revise this limit as applicable. This has been committed to by the applicant and is acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant has committed to analyse the dissolution data from the first three commercial batches of Jayempi 10mg/ml oral suspension and submit a variation to tighten the dissolution specification limit to the level requested by CHMP if the data indicates that it is feasible.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Jayempi manufactured by Nova Laboratories Ireland Limited is considered unlikely to result in any significant increase in the combined sales volumes for all azathioprine containing products and the exposure of the environment to the active substance. Jayempi has been developed to substitute for approved azathioprine oral tablet products.

According to Guideline on the environmental risk assessment of medicinal products for human use (26 May 2016 EMA/CHMP/SWP/44609/2010 Rev. 1), the justification of the absence of significant increase of the environmental exposure, demonstrated by suitable information, can be accepted as a justification for the absence of a complete ERA.

Thus, the impact on the environment is expected to be unchanged.

2.3.3. Discussion on non-clinical aspects

Jayempi containing 10 mg azathioprine per ml of suspension, has been developed to substitute for approved azathioprine oral tablet products. Reference is made to the non-clinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on updated scientific literature. In the CHMP's view, the non-clinical overview adequately justifies that there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Jayempi 10mg/ml oral suspension from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Jayempi 10mg/ml oral suspension containing 10mg azathioprine per ml. To support the marketing authorisation application the applicant conducted a bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for this application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

Clinical studies

To support the application, the applicant has submitted the following bioequivalence study:

Study INV691: 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) in at least 30 healthy adult subjects under fasting conditions.

2.4.2. Pharmacokinetics

Methods

Study design

Study protocol of the comparative bioequivalence study protocol version 1.2 dated 17 January 2019 and was reviewed and approved 22 February 2019 by the North East - York Research Ethics Committee (Newcastle, United Kingdom).

The study was a single dose, open-label, randomised, two period crossover study under fasting conditions, to establish comparative bioequivalence of Jayempi azathioprine suspension 10 mg/mL (Test: manufactured by Nova Laboratories Ireland Limited) and Imurek azathioprine tablet 50 mg (MAH: Aspen Pharma Trading Limited, Dublin, Ireland sourced from Germany). The primary objective of the study was to assess whether oral azathioprine suspension (Jayempi and a marketed tablet formulation (Imurek) were bioequivalent. The secondary objectives were to assess the safety and tolerability of the test product, azathioprine oral 10 mg/mL suspension and to determine the plasma concentrations and pharmacokinetics of the metabolite mercaptopurine.

The study centre was in United Kingdom. The studies were conducted between 15 April 2019 and 17 June 2019. The bioanalytical part was conducted between 25 April 2019 to 24 May 2019.

In line with the set eligibility criteria, all subjects who consented to the study had to undergo thiopurine methyltransferase (TPMT) phenotyping to confirm eligibility and those with a deficient, low or intermediate TPMT enzyme activity were excluded from taking part.

Subjects received either the test (Jayempi azathioprine suspension 10 mg/mL) or reference (Imurek azathioprine tablet 50 mg) product once, according to the randomisation schedule, under fasting conditions. After an overnight fast of at least 10 hours, subjects received either the reference or test product according to the randomisation schedule. The reference investigational medicinal product (Imurek azathioprine tablet 50 mg) was administered with 240 mL of water.

For the solution (test product), 5 mL of the suspension was prepared by drawing up into a syringe for oral administration according to the instructions provided by Nova Laboratories Ltd. The syringe was placed directly into the mouth of the subject and the contents gently released. Immediately after dosing the syringe was rinsed with 5 mL of water which the subject also swallowed, followed by drinking 235 mL of water.

Subjects completed a palatability (taste, aftertaste, smell, texture, ease of use and other comments) questionnaire on the day they received the test (Jayempi azathioprine suspension 10 mg/mL) product.

Pharmacokinetic blood samples were collected at the following times: Blood collections were collected at pre-dose (within 30 minutes before administration) and at 15 mins (±2 mins), 30 mins (±2 mins), 45 mins (±2 mins), 1hr (±2 mins), 1 hr 20 mins (±2 mins), 1 hr 40 mins (±2 mins), 2hrs (±5 mins), 2hrs 20 mins (±5 mins), 2hrs 40 mins (±5 mins), 3hrs (±5 mins), 4hrs (±5 mins), 5hrs (±5 mins), 6hrs (±5 mins), 8hrs (±5 mins), and 12hrs (±5 mins) after study drug administration. The total number of blood collections was 32, 16 samples per period.

Test and reference products

Identity of Investigational Medicinal Products

Table 9.4.1 Identity of Investigational Medicinal Products

IMP	Product Name	Strength	Form	Batch No.	Expiry
Reference Product A	Azathioprine (Jayempi)	10 mg/mL	Oral suspension	NOVPg100	19 July 2019
Reference Product B	Azathioprine (Imurek, Aspen Pharma Trading Limited)	50 mg	Tablet	NOVPg100	28 February 2023

Population(s) studied

There were 30 subjects randomised into the study with a mean age of 37.1 years (SD: 9.88) and comprising 19 male (63.3%) and 11 female (36.7%) subjects. The subjects were predominantly White (90.0%). All subjects were analysed in the safety analysis set and all but one subject in the Tablet 50 mg/Suspension 10 mg/mL treatment sequence (Tablet 50 mg group) was excluded from the PK set: Subject 001/029, who did not complete the study because he withdrew consent.

Subjects were selected according to the inclusion and exclusion criteria in order to obtain a low individual variability within the subject group. Subjects who met all the inclusion and none of the exclusion criteria were enrolled into the study.

The inclusion criteria were as follows:

- Healthy male and female subjects, 18 years to 50 years inclusive at time of signing the informed consent form.

- Females of childbearing potential with a negative pregnancy test at screening and willing to use a condom plus 1 highly effective method of contraception from first dose until 6 months after last dose of IMP.
- Females of non-childbearing potential, defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries or post-menopausal females defined as being at least 45 years of age with a history of amenorrhoea for 12 months without an alternative medical reason.
- Male subjects willing to use 2 highly effective methods of contraception from the first IMP dose until 6 months after the last IMP dose.
- Body mass index (BMI) between 18 and 33 kg/m^2.
- Body weight not less than 50 kg.
- Subjects with no clinically significant abnormal serum biochemistry, haematology and urine examination values within 28 days before the first IMP dose.
- Medical history, physical examination, standard 12-lead electrocardiogram (ECG) and vital signs investigations: Findings clinically acceptable or within reference ranges, unless the investigator considered the deviation irrelevant for the purpose of the study.
- Non-smokers.

Other than oral contraception, subjects had to refrain from using any medication, prescribed or over-the-counter (including herbal remedies, St. John's wort [hypericum perforatum]) for 2 weeks before the first IMP dose and for the duration of the study. Occasional use of paracetamol ≤2 g/day and/or ibuprofen (≤1200 mg/day) was allowed for pain.

Analytical methods

Analysis was conducted using a validated high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (number 0001/117). The method was validated prior to sample analysis.

The applicant provided a full bioanalytical report, including the analysis results for calibration standards, quality control samples, study samples, and incurred sample reanalysis, in compliance with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Study samples: Receipt, Storage and Analysis

A total of 944 human plasma samples (plus 944 back up samples) from Sponsor Study Number INV691 were received frozen on dry ice and in good condition from 21 May 2019 to 30 May 2019 for analysis. All samples were stored at a nominal temperature of -80°C until analysed and were returned to these storage conditions post-analysis. Sample analysis was performed from 28 May 2019 to 14 Jun 2019.

The analytical procedure involved extraction of azathioprine and 6-mercaptopurine in human plasma using protein precipitation extraction followed by separation. LC-MS/MS was performed using a mass spectrometer (MS) with ultra high performance liquid chromatography (UHPLC) system running software and using quantitation software.

The date of the first sample collection was 25 April 2019. The date of the last sample extraction was 12 June 2019. Based on the number of days from the first sample collection date and last sample extraction date, samples were stored at a nominal temperature of -80°C for a maximum of 48 days.

All samples were analysed within the determined storage stability period of 91 days for azathioprine and 171 days for 6-mercaptopurine at a nominal temperature of -80°C.

Bioanalytical report

The bioanalytical report was submitted (0001/117 report version 02 dated 28 May 2019) with 20% of the subject chromatograms. Azathioprine-d3 and 6-mercaptopurine-13C2,15N (sourced from Toronto Research Chemicals) were used as the internal standards for the determination of azathioprine and 6-mercaptopurine concentrations in human plasma samples, respectively. Certificates of analysis for the reference and internal standards of azathioprine, 6-mercaptopurine, azathioprine-d3 and 6-mercaptopurine-13C2,15N have been provided and are deemed acceptable.

Calibration standards (at 9 different concentrations) and quality controls samples were prepared according to the sample analysis plan and contained azathioprine and 6-mercaptopurine. All concentrations were back-calculated from calibration curves generated from lines fitted through the standard data points with a nominal concentration range of 0.200 ng/mL to 100 ng/mL for azathioprine and 6-mercaptopurine from 100 µL human plasma. Standards were injected in ascending order with one standard curve at the beginning of the run and a duplicate STD1 and STD9 injected in descending order at the end of the run. Quality control samples were injected throughout the run and bracketed study sample injections.

Overall precision for the quality control samples, as measured by % coefficient of variation, was ≤4.00% for azathioprine and ≤4.60% for 6-mercaptopurine. The overall accuracy (% deviation from nominal) as measured by % relative error, for these quality control samples ranged from 96.1% to 100% for azathioprine and 97.0% to 102% for 6-mercaptopurine.

Repeat analysis

The following tables show the number of samples re-assayed for azathioprine and 6-mercaptopurine. The calculated concentrations and reasons for the repeat analysis were provided.

Repeat Analysis Results for azathioprine in human plasma

Subject number	Treatment Period, Time point	Original Concentration (ng/mL)	Original analysis batch	Reason for repeat	Repeat concentrations ng/mL (duplicate analysis)	Repeat analysis batch	Reported Concentration (ng/mL)
1021	TP1, 2Hour 40	BLQ	5	Unexpected low concentration, agreed with client	3.68, 3.72	7	3.68 (median value)

Repeat Analysis Results for 6-mercaptopurine in human plasma

Subject number	Treatment Period, Time point	Original Concentration (ng/mL)	Original analysis batch	Reason for repeat	Repeat concentrations ng/mL (duplicate analysis)	Repeat analysis batch	Reported Concentration (ng/mL)
1021	TP1, 2Hour 40	0.783	5	Unexpected low concentration, agreed with client	3.26, 3.23	7	3.23 (median value)

Incurred Sample Reanalysis (ISR)

A total of 96 human plasma samples were identified for incurred sample reanalysis. ISR samples were selected according to the following approximate distribution:

- 4% of the samples near the Cmax of azathioprine
- 3% near the Cmax of 6-mercaptopurine
- 3% in the late phase of azathioprine

For acceptance, the agreement between the original and the repeat value had to be within ±20% of the mean result for two-thirds of the repeated samples. The acceptance criterion was met for azathioprine since 96/96 (100%) ISR samples had results within 20% of their mean value. The acceptance criterion was met for 6-mercaptopurine since 95/96 (99.0%) ISR samples had results within 20% of their mean value.

Validation of the test method

The applicant has declared that the method was validated prior to sample analysis giving reference to validation results provided in Analytical Study Number 0030/001 (Section 12 Reference 1 - Validation of a Bioanalytical Method for the Determination of Azathioprine and 6-Mercaptopurine in Human Plasma with K2EDTA by LC-MS/MS. Study Number 0030/001).

Pharmacokinetic variables

Primary PK: Maximum observed concentration (Cmax), area under the concentration-time curve from time of dosing to last quantifiable concentration (AUC0-τ) and AUC extrapolated to infinity (AUC0-∞)

Secondary PK: Time to Cmax (Tmax), terminal elimination rate constant (λz) and t½.

Statistical methods

Pharmacokinetic data of 29 subjects, who completed the study, were included for statistical analysis.

The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the C_{max} and AUC_{0-T} was based on ln-transformed data.

ANOVA model: fixed factors: sequence, subject nested within sequence, product and period effects after logarithmic transformation of the data.

Criteria for Bioequivalence: Statistical inference of azathioprine was based on a bioequivalence approach using the following standards:

The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-T} were all within the 80.00 to 125.00% bioequivalence range.

All statistical analysis was performed using SAS® version 9.4.

Results

The applicant presented a full report on the results of the study, including azathioprine concentrations for each sampling time, phase and subjects.

A single centre, randomised, single dose, 2-period crossover bioequivalence study was conducted under fasting conditions on 30 healthy male and female subjects. The rate and extent of absorption of azathioprine were measured and compared following a single dose of the Test (1 x 50 mg) and of the Reference formulation (1 x 5 mL).

Summary of plasma pharmacokinetic parameters (Study INV691) - azathioprine

Parameter (unit)	Statistics	Oral Azathioprine		
		Tablet 50 mg (N=29)	Suspension 10 mg/mL (N=29)	'Suspension': 'Tablet'
Cmax (ng/mL)	n	29	29	29
	Mean	17.8	19.65	1.338
	SD	8.913	9.656	0.8961
	Geometric Mean	15.49	17.35	1.121
	Geometric CV%	61.7	56.4	63.5
	Minimum	4.4	5.7	0.49
	Median	16.3	17.3	0.992
	Maximum	39.5	40	3.75
AUC_{0-t} (h.ng/mL)	n	29	29	29
	Mean	18.12	19.18	1.081
	SD	7.2	7.455	0.1911
	Geometric Mean	17.1	18.17	1.063
	Geometric CV%	33.8	32.1	19.3
	Minimum	10.3	11	0.53
	Median	16.2	17.1	1.061
	Maximum	44	46.8	1.52
$AUC_{0-\infty}$ (h.ng/mL)	n	23	26	22
	Mean	18.37	19.98	1.033
	SD	5.494	7.686	0.1559
	Geometric Mean	17.71	18.96	1.019
	Geometric CV%	27.1	31.6	18.2
	Minimum	12	13.7	0.52
	Median	16.4	17.8	1.037
	Maximum	33.5	47.3	1.31
$t_{1/2}$ (h)	n	23	26	
	Mean	0.484	0.36	
	SD	0.2894	0.158	
	Geometric Mean	0.427	0.336	
	Geometric CV%	51.4	37.2	
	Minimum	0.21	0.21	
	Median	0.39	0.315	
	Maximum	1.36	0.91	

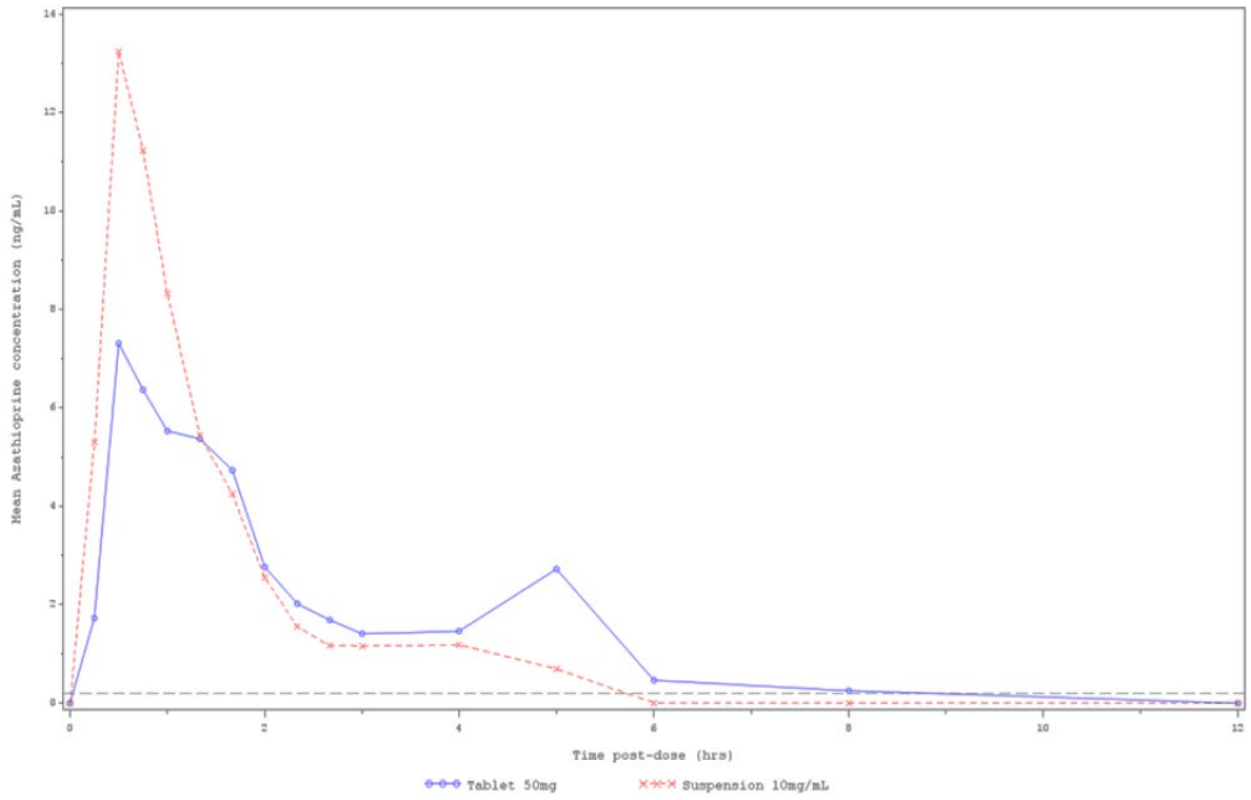
Summary of plasma pharmacokinetic parameters (Study INV691) 6-mercaptopurine

Parameter (unit)	Statistics	Oral Azathioprine		
		Tablet 50 mg (N=29)	Suspension 10 mg/mL (N=29)	'Suspension': 'Tablet'
Cmax (ng/mL)	n	29	29	29
	Mean	17.85	18.29	1.201
	SD	9.606	8.264	0.7011
	Geometric Mean	15.72	16.49	1.049
	Geometric CV%	54.5	50.8	55.5
	Minimum	5.8	5.5	0.43
	Median	15.6	17.6	0.977
	Maximum	42.2	43.4	3.8
AUC_{0-t} (h.ng/mL)	n	29	29	29
	Mean	39.54	39.82	1.03
	SD	16.402	17.034	0.2567
	Geometric Mean	36.77	36.79	1.001
	Geometric CV%	39.4	41.4	24.8
	Minimum	18.9	19.4	0.67
	Median	35.9	36.8	0.995
	Maximum	80.1	88.2	1.52
$AUC_{0-\infty}$ (h.ng/mL)	n	28	29	28
	Mean	40.97	40.4	1.027
	SD	16.175	17	0.2553
	Geometric Mean	38.38	37.44	0.997
	Geometric CV%	36.9	40.5	24.9
	Minimum	20.3	20.1	0.67
	Median	37.5	37.1	0.983
	Maximum	80.7	88.8	1.49
$t_{1/2}$ (h)	n	28	29	
	Mean	1.221	1.225	
	SD	0.3217	0.2789	
	Geometric Mean	1.189	1.197	
	Geometric CV%	22.5	21.4	
	Minimum	0.86	0.84	
	Median	1.165	1.14	
	Maximum	2.35	1.88	

Analysis of variance of plasma PK parameters of azathioprine (Study INV691)

Parameter	Statistics	Oral Azathioprine	
		Tablet 50 mg (N=29)	Suspension 10 mg/mL (N=29)
Cmax (ng/mL)	Number of subjects included in analysis	29 (100.0)	29 (100.0)
	Ratio ('Suspension' : 'Tablet')		
	Point estimate		1.12
	p-value		0.3008
	90% CI		0.93, 1.35
AUC_{0-t} (h.ng/mL)	Number of subjects included in analysis	29 (100.0)	29 (100.0)
	Ratio ('Suspension' : 'Tablet')		
	Point estimate		1.06
	p-value		0.1061
	90% CI		1.00, 1.13
$AUC_{0-\infty}$ (h.ng/mL)	Number of subjects included in analysis	23 (79.3)	26 (89.7)
	Ratio ('Suspension' : 'Tablet')		
	Point estimate		1.02
	p-value		0.5696
	90% CI		0.96, 1.09

Mean plasma concentration time curve of azathioprine in linear scale following single oral dose of Azathioprine (n=29)



Intra-subject variability of plasma pharmacokinetic parameters of azathioprine (Study INV691)

Parameter	Statistics	Oral Azathioprine
		All Subjects (N=29)
Cmax	Number of subjects included in analysis n (%)	29 (100.0)
	%Coefficient of variation	43.62
AUC(0-tau)	Number of subjects included in analysis n (%)	29 (100.0)
	%Coefficient of variation	13.78
AUC(0-infinity)	Number of subjects included in analysis n (%)	27 (93.1)
	%Coefficient of variation	12.57

Safety data

In the bioequivalence study carried out (INV691) to establish comparative bioequivalence of Jayempi azathioprine suspension 10 mg/mL (Test: manufactured by Nova Laboratories Ireland Limited) and Imurek® azathioprine tablet 50 mg (MAH: Aspen Pharma Trading Limited, Dublin, Ireland sourced from Germany):

There were no subjects with a serious treatment-emergent adverse event (TEAE) or TEAEs leading to withdrawal from study or discontinuation from the investigational medicinal product. There were no subjects with any severe TEAEs.

Adverse events: Safety analysis set

There were 3 subjects with a moderate severity TEAE. Subject 001/040 had 11 hours of moderate vomiting starting from 8 hours 14 minutes after azathioprine tablet, which was considered not IMP related and sufficiently long after administration not to affect PK or merit exclusion from the PK analysis set. Subject 001/021 had moderate labyrinthitis after azathioprine suspension, which was considered unlikely IMP related and Subject 001/037 had moderate gastroenteritis, which was considered not IMP related.

Treatment-emergent adverse events

System Organ Class Preferred Term	Azathioprine Tablet N=30 n (%)	 Suspension N=29 n (%)
Subjects With at least 1 TEAE	6 (20.0)	7 (24.1)
Infections and infestations	2 (6.7)	2 (6.9)
Gastroenteritis	0	1 (3.4)
Hordeolum	1 (3.3)	0
Labyrinthitis	0	1 (3.4)
Oral herpes	1 (3.3)	0
Gastrointestinal disorders	2 (6.7)	1 (3.4)
Diarrhoea	0	1 (3.4)
Nausea	1 (3.3)	0
Vomiting	1 (3.3)	0
Nervous system disorders	2 (6.7)	1 (3.4)
Headache	2 (6.7)	1 (3.4)
General disorders and administration site conditions	0	2 (6.9)
Catheter site hypoaesthesia	0	1 (3.4)
Catheter site mass	0	1 (3.4)
Renal and urinary disorders	1 (3.3)	1 (3.4)
Chromaturia	1 (3.3)	1 (3.4)
Blood and lymphatic system disorders	0	1 (3.4)
Lymphadenopathy	0	1 (3.4)
Injury, poisoning and procedural complications	1 (3.3)	0
Contusion	1 (3.3)	0
Psychiatric disorders	1 (3.3)	0
Euphoric mood	1 (3.3)	0

TEAE, treatment-emergent adverse event
Source: Table 14.3.1.2

There were 2 subjects with a treatment-related TEAE (pooled category). Subject 001/011 had mild chromaturia after azathioprine tablet and suspension, which was considered possibly IMP related and Subject 001/015 had mild nausea after azathioprine tablet, which was considered probably/likely IMP related.

There were no clinically significant haematology or biochemistry changes for any subject. There were no clinically significant findings during assessments of vital signs, physical examinations or 12-lead ECGs.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

A general statement has been provided (INV691-16-1 section 4.1) from the principal investigator, signed and dated 17 January 2019 declaring that the study has been carried out in line with GCP, Ethics Approval and Quality Control. The applicant declared that no audits have been carried out,

however compliance with the Quality Management System was confirmed. Site was also inspected by MHRA with a positive GCP compliance inspection report.

On test and reference products used in the clinical study batch numbers, batch size and assay results have been provided by the applicant.

The population studied is adequate and well characterised for the purpose of the study. The main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01).

The sample size calculation was determined to be 30 subjects, to produce at least 28 evaluable subjects, allowing for those who withdraw or otherwise fail to complete the study. The sample size was selected without any formal statistical considerations. The applicant selected the sample size in line with other similar bioequivalence studies by referring to Public Assessment Reports. The applicant supported the sample size selection with literature references. The sample size (29 subjects) used for statistical analysis was enough to support the power of the study as 24 subjects were needed to have a power of more than 85%. One dropout is considered not to have an impact on the study.

The analytical methods used are acceptable and appropriate. The chromatograms presented are acceptable. The calibration curves are appropriate. The applicant has provided the results were the concomitant medications have been accounted for in the bioanalytical method. No effect on the determination of the analyte and the internal standard was observed.

Twenty percent (20%) of the chromatograms have been provided in line with the Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 rev. 1 corr.2**. The incurred sample reanalysis was provided and is acceptable.

The applicant provided the validation of the bioanalytical method document 'Validation of a Bioanalytical Method for the Determination of Azathioprine and 6-Mercaptopurine in Human Plasma with K2EDTA by LC-MS/MS. Validation results are acceptable. The analytical methods were audited, and a signed statement dated 22 October 2019 was provided. The pharmacokinetic methods and variables are adequate for the purpose of this study.

In line with the clinical pharmacology and pharmacodynamics included in the SmPC of the reference product, the bioequivalence study design and sampling periods are acceptable, with an adequate wash-out period at greater than 5 times the t½ (3-5 hours). The SmPC states that azathioprine should be taken at least 1 hour before or 2 hours after a meal or milk, hence in line with the Guideline for Bioequivalence a fasting study is appropriate. The sampling frequency enabled an adequate estimation of Cmax.

The applicant explained that the population studied (healthy volunteers) was rigorously screened since there are individuals with an inherited deficiency of the enzyme TPMT who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with azathioprine. It has also been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics. All subjects who gave consent to the study underwent TPMT phenotyping and those with a deficient, low or intermediate TPMT enzyme activity were excluded from taking part.

With respect to the palatability testing questionnaire performed after the study, most subjects found the taste, smell and texture of the liquid to be fairly good or good, with median scores for subjects' assessment being around 74 to 85 mm on the visual analogue scale. Most (69%) did not detect an aftertaste. The majority of subjects responded positively (median score 94 mm out of 100mm length) to being asked if they would find it easy to take it every day.

The statistical methods employed are in compliance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

Criteria were prospectively set for Cmax and AUC following the guidance on bioequivalence (CPMP/EWP/QWP/1401/98 rev.1) i.e. that the Cmax, AUC0-t and AUC0-∞ 90% confidence intervals should be contained within the range 80% - 125%. The 90% confidence intervals for AUC0-T falls within the 80.00%-125.00% range. On the other hand, the upper limit of the 90% confidence interval for Cmax was 135% exceeding the acceptance interval of 80.00%-125.00%. These results show that the test product is not bioequivalent for Cmax according to the set parameters of bioequivalence in the protocol. This was discussed in the Clinical Overview where the applicant concluded that this deviation from the protocol is due to substantial intra-subject variability (CV is 43.64%).

Results also show that the average Cmax was approximately 12% higher with the oral suspension compared to the tablet. The applicant discussed this in the Clinical Overview where it was stated that there was virtually no difference between the two formulations in the maximum Cmax value observed, reflecting the high inter-subject variability in Cmax. Thus, data from the current bioequivalence study suggests that in practice that there is unlikely to be a significant difference between the two formulations with respect to the highest individual Cmax values achieved within a population. Further to the above, the applicant discussed the implications of the different pharmacokinetic characteristics of the oral suspension as compared to the tablet on the safety and efficacy of the oral suspension. Scientific literature was provided to support that there is no clinically relevant difference expected between the two formulations of azathioprine, as a result of the higher Cmax, based on azathioprine pharmacology, including pharmacokinetics of the intravenous formulation.

Overall, the drugs tested were generally safe and well tolerated by the subjects (male and female) included in this study and no new safety concerns were raised during the conduct of the study.

The applicant is proposing two dosing syringes (a red syringe graduated to 3 ml and a white syringe graduated to 12 ml) which are provided for accurate measurement of the prescribed dose of the oral suspension. The use of two different colours for the syringes to make them distinguishable was not considered sufficient by the CHMP to minimise the risk of medication errors and on request of the committee the applicant added further instructions in 4.2 of the SPC on range of doses, age and weight, the dose (mg) to volume (ml) conversion using the two oral syringes to avoid dispensing errors the package leaflet was updated accordingly. The dosing schedule gives now clear instructions and covers dosing in mg and ml respectively, according to age and weight from 0-18 years, and which syringe is more appropriate. This is expected to reduce further to risk of medication errors. Furthermore, a follow-up questionnaire on cases of medication errors was included in the pharmacovigilance plan. To strengthen monitoring of medication errors specifically due to the conversion from tablets to liquid formulation and two syringes the applicant committed to submit annual reports with data lock points synchronised with the data of authorisation as outlined in the RMP as category 3 additional pharmacovigilance activity.

Further to all the above amendments in relation to the conversion of patients from tablet to liquid formulation and provision of two dosing syringes, the additional measures to minimise the risk of medication errors are considered acceptable by the CHMP.

The applicant took also the opportunity to update the Product Information in accordance with the PRAC outcome on Azathioprine - Erythema Nodosum - EPITT 19623 (PRAC April 2021) and included erythema nodosum in 4.8 of the SmPC under "immune system disorders" the Package leaflet was updated in accordance.

2.4.6. Conclusions on clinical aspects

The applicant performed a comparative bioequivalence study (INV691) between Jayempi 10 mg/mL oral suspension and Imurek 50 mg tablets. Criteria were prospectively set for Cmax and AUC following the guidance on bioequivalence (CPMP/EWP/QWP/1401/98 rev.1) i.e. that the Cmax, AUC0-t and AUC0-∞ 90% confidence intervals should be contained within the range 80% - 125%. The pharmacokinetic statistical analysis showed that upper limit of the 90% confidence interval for Cmax was 135%, which exceeds the acceptance interval of 80.00%-125.00% set in the protocol. These results show that the test product is not bioequivalent for Cmax according to the set parameters of bioequivalence in the protocol, however considering that a different formulation than the reference product is submitted under the legal basis article 10(3) (hybrid application) no strict bioequivalence is required. Results showed that the average Cmax was approximately 12% higher with the oral suspension compared to the tablet. The applicant discussed the implications of the different pharmacokinetic characteristics of the oral suspension as compared to the tablet on the safety and efficacy of the oral suspension. Scientific literature was provided which support that there is no clinically relevant difference expected between the two formulations of azathioprine, as a result of the higher Cmax. This was considered acceptable to the CHMP.

The applicant implemented adequate wordings in 4.2 of the SmPC and package leaflet in order to minimise the risk or medication errors. Annual reports on medication errors will be provided outside of PSURs as outlined in the RMP.

2.5. Risk Management Plan

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: 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.
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		

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The applicant submitted a full user testing report complemented by a Focus test report after implementing the package leaflet during the procedure with improved instructions on how to use the product.

The results of the user consultation submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a hybrid version of azathioprine oral suspension. The reference product Imurek is indicated for all indications claimed by the applicant. No new non-clinical studies have been provided for this application and reference is made to the non-clinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date scientific literature. In the CHMP's opinion, the non-clinical overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data which is considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient by the CHMP.

The bioequivalence study forms the pivotal basis with 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) in at least 30 healthy adult subjects under fasting conditions.

The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with European requirements. The SmPC states that azathioprine should be taken at least 1 hour before or 2 hours after a meal or milk, hence in line with the Guideline for Bioequivalence a fasting study is appropriate. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Jayempi did not meet the protocol-defined criteria for bioequivalence when compared with the Imurek. The pharmacokinetic statistical analysis showed that upper limit of the 90% confidence interval for Cmax was 135%, which exceeds the acceptance interval of 80.00%-125.00% set in the protocol. These results show that the test product is not bioequivalent for Cmax according to the set parameters of bioequivalence in the protocol. Results showed that the average Cmax was approximately 12% higher with the oral suspension compared to the tablet.

The applicant discussed the implications of the different pharmacokinetic characteristics of the oral suspension as compared to the tablet on the safety and efficacy of the oral suspension. Scientific literature was provided and it is agreed with the applicant that in view of the high inter and intra-subject variability and the result from the bioequivalence study showing no real difference in the observed metabolite 6-MP Cmax values with both formulations (geometric mean ratio = 1.05) there are no reasons to support the view that differences in minimally elevated mean Cmax with Jayempi will lead to a clinical relevant difference compared to the tablet formulation in clinical practice. Considering that a different formulation than the reference product is submitted under the legal basis article 10(3) (hybrid application) no strict bioequivalence is required and the justification that the difference in bioequivalence is not clinically relevant can be accepted by the CHMP. As outlined in 4.2 of the SmPC the therapy with Jayempi should be initiated by a physician experienced in the administration and monitoring of immunosuppressive medicinal products. Therefore, the CHMP agreed with the applied prescription status subject to restricted medical prescription.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

From a Quality aspect, the applicant has adequately addressed all the major objections and concerns which were raised and is approvable. The applicant has committed to analyse the dissolution data from the first three commercial batches of Jayempi 10mg/ml oral suspension, and submit a variation to tighten the dissolution specification limit to NLT Q=85% at 15 minutes if the data indicates that it is feasible.

A positive benefit/risk ratio can be concluded.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Jayempi is not similar to Soliris within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jayempi is favourable in the following indications:

Jayempi is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic 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 drugs – DMARDs)

- auto-immune hepatitis
- systemic lupus erythematosus
- dermatomyositis
- polyarteritis nodosa
- pemphigus vulgaris and bullous pemphigoid
- Behçet's disease
- refractory auto-immune haemolytic anaemia, caused by warm IgG 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 adult patients 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the

agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable