

Public Assessment Report

Scientific discussion

Trispan 20 mg/ml, suspension for injection (triamcinolone hexacetonide)

NL/H/4631/001/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Trispan 20 mg/ml, suspension for injection. The procedure was finalised in the United Kingdom (UK/H/4817/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Public Assessment Report

Decentralised Procedure

TRIAMCINOLONE HEXACETONIDE 20 MG/ML SUSPENSION FOR INJECTION

(triamcinolone hexacetonide)

Procedure No: UK/H/4817/001/DC

UK Licence No: PL 17509/0061

Intrapharm Laboratories Limited

LAY SUMMARY

Triamcinolone Hexacetonide 20 mg/ml suspension for injection (triamcinolone hexacetonide)

This is a summary of the public assessment report (PAR) for Triamcinolone Hexacetonide 20 mg/ml suspension for injection (PL 17509/0061). It explains how Triamcinolone Hexacetonide 20 mg/ml suspension for injection was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Triamcinolone Hexacetonide 20 mg/ml suspension for injection.

For practical information about Triamcinolone Hexacetonide 20 mg/ml suspension for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Triamcinolone Hexacetonide 20 mg/ml suspension for injection and what is it used for?

This application for triamcinolone Hexacetonide 20 mg/ml suspension for injection is a hybrid application. This means that Triamcinolone Hexacetonide 20 mg/ml suspension for injection is similar to a 'reference medicine' already authorised in the European Union (EU) called Lederspan 20 mg/ml suspension for injection and can be used for the same indications. Additionally, suitable data have been submitted to support its use in a further indication of juvenile idiopathic arthritis (JIA).

Triamcinolone Hexacetonide 20 mg/ml suspension for injection is an injection which contains a steroid medicine. Steroids are similar to a type of hormones that are made naturally in the adrenal gland of the body. Triamcinolone Hexacetonide 20 mg/ml suspension for injection is given to adults and or adolescents for the treatment of joint pain, swelling and stiffness in subacute and chronic inflammatory joint diseases including rheumatoid arthritis, JIA (arthritis in children), osteoarthritis (a joint disease caused by wear and tear), post-traumatic arthritis and synovitis (mild swelling of the tissues around the joint), tendinitis (inflammation of a tendon), bursitis (inflammation of one or more bursae (small fluid-filled sacs) of synovial fluid in the body) and epicondylitis (lateral elbow pain, also known as tennis elbow). Triamcinolone Hexacetonide 20 mg/ml suspension for injection is also used for the intraarticular use (injection into the joint) in children aged 3-12 years with juvenile idiopathic arthritis.

How is Triamcinolone Hexacetonide 20 mg/ml suspension for injection used?

This medicine can only be obtained with a prescription.

How does Triamcinolone Hexacetonide 20 mg/ml suspension for injection work?

Triamcinolone Hexacetonide 20 mg/ml suspension for injection is injected into and around the joints which results in an anti-inflammatory effect. Triamcinolone Hexacetonide 20 mg/ml suspension for injection must not be administered into a vein, into the skin, below the skin, into the muscle, into the eyes, into the spinal canal or into the brain or spinal cord. Triamcinolone Hexacetonide 20 mg/ml suspension for injection may be mixed with 1% or 2% lidocaine hydrochloride or other similar local anaesthetics.

How has Triamcinolone Hexacetonide 20 mg/ml suspension for injection been studied?

This application for Triamcinolone Hexacetonide 20 mg/ml suspension for injection is a hybrid application, claiming to be bioequivalent to the reference medicinal product Lederspan 20 mg/ml suspension for injection. The physico-chemical characteristics for Triamcinolone Hexacetonide 20 mg/ml suspension for injection and the reference product Lederspan 20 mg/ml suspension for injection have been demonstrated to show that the two medicines produce the same levels of the active substance in the body

What are the benefits and risks of Triamcinolone Hexacetonide 20 mg/ml suspension for injection?

This application for triamcinolone Hexacetonide 20 mg/ml suspension for injection is a hybrid application and the product is bioequivalent to the reference medicine. Therefore, their benefits and risks are taken as being the same as the reference medicines.

Why is Triamcinolone Hexacetonide 20 mg/ml suspension for injection approved?

It was concluded that, in accordance with EU requirements, Triamcinolone Hexacetonide 20 mg/ml suspension for injection have been shown to have comparable quality and physico-chemical characteristics to Lederspan 20mg/ml suspension for injection. Therefore, the view was that, as for Lederspan 20 mg/ml suspension for injection, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Triamcinolone Hexacetonide 20 mg/ml suspension for injection?

A risk management plan has been developed to ensure that Triamcinolone Hexacetonide 20 mg/ml suspension for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Triamcinolone Hexacetonide 20 mg/ml suspension for injection approved, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Triamcinolone Hexacetonide 20 mg/ml suspension for injection

Austria, Czech Republic, Portugal, Slovenia, Spain, The Netherlands and the UK agreed to grant a Marketing Authorisation for Triamcinolone Hexacetonide 20 mg/ml suspension for injection on 28 November 2013. A Marketing Authorisation was granted in the UK on 24 December 2013.

The full PAR for Triamcinolone Hexacetonide 20 mg/ml suspension for injection follows this summary. For more information about treatment with Triamcinolone Hexacetonide 20 mg/ml suspension for injection, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in 02-2014.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 5
Module 2: Summary of Product Characteristics	Page 6
Module 3: Patient Information Leaflet	Page 7
Module 4: Labelling	Page 8
Module 5: Scientific discussion during initial procedure	Page 10
I Introduction	
II About the product	
III Scientific overview and discussion	
III.1 Quality aspects	
III.2 Non-clinical aspects	
III.3 Clinical aspects	
IV Overall conclusion and benefit-risk assessment	
Module 6: Steps taken after initial procedure	Page 18

Module 1

Information about initial procedure

Product Name	Triamcinolone Hexacetonide 20 mg/ml suspension for injection
Type of Application	Hybrid, Article 10(3)
Active Substances	Triamcinolone Hexacetonide
Form	Suspension for injection
Strength	20 mg/ml
MA Holder	Intrapharm Laboratories Ltd. The Courtyard Barns Choke Lane Maidenhead Berkshire, SL6 6PT United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Austria, Czech Republic, Portugal, Slovenia, Spain, The Netherlands
Procedure Number	UK/H/4817/001/DC
Timetable	Day 210 – 28 November 2013

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3

Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflet for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folding box

1. NAME OF THE MEDICINAL PRODUCT

TRIAMCINOLONE HEXACETONIDE 20 mg/ml suspension for injection

Triamcinolone hexacetonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ampoule with 1 ml suspension for injection contains 20 mg triamcinolone hexacetonide

3. LIST OF EXCIPIENTS

Excipients:

9 mg benzyl alcohol; polysorbate 80, sorbitol (E420), water for injection

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 ampoules with 1 ml suspension for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intra-articular use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

Expiry date:

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Intrapharm Laboratories Ltd.
The Courtyard Barns
Choke Lane
Maidenhead
Berkshire
SL6 6PT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 17509/0061

13. BATCH NUMBER

Batch No.:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

Shake well before use.

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member state considered that the application for Triamcinolone Hexacetonide 20 mg/ml suspension for injection (PL 17509/0061; UK/H/4817/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Czech Republic, Portugal, Slovenia, Spain and The Netherlands as Concerned Member States (CMS).

This product can only be obtained with a prescription (legal classification POM). It is indicated for intraarticular, intrasynovial or periarticular use in adults and adolescents for the symptomatic treatment of subacute and chronic inflammatory joint diseases including:

- Rheumatoid arthritis
- Juvenile Idiopathic Arthritis (JIA)
- Osteoarthritis and post-traumatic arthritis
- Synovitis, tendinitis, bursitis and epicondylitis

This application was made under the Decentralised Procedure (DCP), according to Article 10(3) of Directive 2001/83/EC, as amended, claiming essential similarity to Lederspan 20 mg/ml suspension for injection (Meda Oy Limited), which was granted a marketing authorisation in Finland on 15 August 1994 (PL 00053/0064). The UK does not have a suitable, marketed reference product and has accepted the use of the European reference product after consultation with the Finnish regulatory authorities on the suitability of Lederspan 20 mg/ml suspension for injection.

Triamcinolone Hexacetonide 20 mg/ml suspension for injection contains the active substance triamcinolone hexacetonide and is a synthetic glucocorticoid with a pronounced anti-inflammatory effect and minimal mineralocorticoid activity, therefore no sodium retention occurs. Triamcinolone Hexacetonide 20 mg/ml suspension for injection is a microcrystalline anti-inflammatory activity. The anti-inflammatory potency of triamcinolone hexacetonide on a milligram by milligram comparison is approximately five times that of hydrocortisone. Triamcinolone Hexacetonide 20 mg/ml suspension for injection is indicated for intraarticular, intrasynovial or periarticular use in adults and adolescents for the symptomatic treatment of subacute and chronic inflammatory joint diseases; which include, rheumatoid arthritis, juvenile idiopathic arthritis (JIA), osteoarthritis and post-traumatic arthritis, synovitis, tendinitis, bursitis and epicondylitis.

No non-clinical studies were submitted, which is acceptable given that the application was a hybrid application, with the product claiming to be bioequivalent to a reference product that has been licensed for over 10 years.

There are no bioequivalence studies or any other new clinical studies submitted for this application. The application has been made based on a “biowaiver” justification. The applicant has provided a justification which is fully supported by the pharmaceutical comparability of the proposed product and the reference product, which is considered adequate to support the biowaiver claim for this application.

The MHRA is satisfied with respect to the pharmaceutical equivalence of this product and its reference product, based on consideration of bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.) which does not mention parenteral locally acting suspension products, but makes allowance for intravenously administered bi-phasic emulsions to be considered on a case-by-case basis.

The evidence provided is considered adequate to support the grant of a marketing authorisation for Triamcinolone Hexacetonide 20 mg/ml suspension for injection with the same indications as those for the reference product Lederspan 20 mg/ml suspension for injection. In addition, suitable literature reviews have been submitted for the approval of the additional indication of juvenile idiopathic arthritis (JIA).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 28 November 2013. After a subsequent national phase, a licence was granted in the UK on 24 December 2013.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Triamcinolone Hexacetonide 20 mg/ml suspension for injection
Name(s) of the active substance(s) (INN)	Triamcinolone Hexacetonide
Pharmacotherapeutic classification (ATC code)	Corticosteroids for systemic use, glucocorticoids (H02AB08)
Pharmaceutical form and strength(s)	20 mg/ml suspension for injection
Reference numbers for the Decentralised Procedure	UK/H/4817/001/DC
Reference Member State	UK
Member States concerned	Austria, Czech Republic, Portugal, Slovenia, Spain, The Netherlands
Marketing Authorisation Number(s)	PL 17509/0061
Name and address of the authorisation holder	Intrapharm Laboratories Ltd. The Courtyard Barns Choke Lane Maidenhead Berkshire, SL6 6PT United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

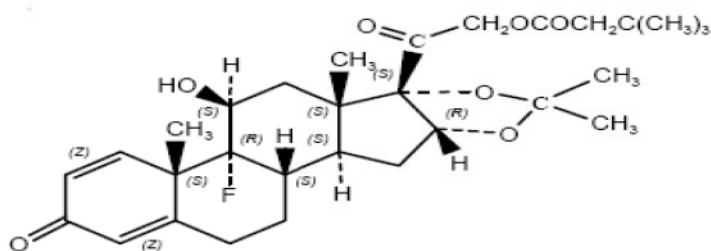
III.1 QUALITY ASPECTS

S. Active substance – Triamcinolone Hexacetonide

rINN: Triamcinolone hexacetonide

Chemical name: 9-Fluoro-11 β -hydroxy-16 α ,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-diene-21-yl 3,3-dimethylbutanoate - Pregna-1,4-diene-3,20-dione, 21-(3,3-dimethyl-1-oxobutoxy)-9-fluoro-11-hydroxy-16,17-[(1-ethylethylidene)bis(oxy)]-(11 β ,16 α)-9 α -Fluoro-11 β ,16 α , 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone 21-(3,3-dimethylbutyrate)

Structure:



Molecular formula: C₃₀H₄₁FO₇

Molecular weight: 532.6

Appearance: white or almost white, microcrystalline powder

Solubility: Practically insoluble in water, sparingly soluble in ethanol and in methanol, soluble in chloroform

Synthesis of the active substance from the designated starting material has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate specifications are provided for the active substance triamcinolone hexacetonide, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory specifications have been provided for all packaging used for storing triamcinolone hexacetonide. The primary packaging has been shown to comply with current legislation concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable. A suitable retest period has been set based on stability data submitted for the active substance stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, as follows:

Liquid sorbitol (E420), polysorbate 80, benzyl alcohol and water for injection.

All excipients used comply with their respective European Pharmacopoeia monographs.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce a suspension for injection containing 20 mg/ml triamcinolone hexacetonide that could be considered as a hybrid medicinal product of the reference product Lederspan 20 mg/ml suspension for injection (Meda Oy Limited). Comparative physico-chemical characteristics have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference product.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of finished product. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged into cartons containing 1 ml colourless Type I glass ampoules in pack sizes of 10 ampoules.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months, with no special storage conditions.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as

amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form

The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary (Expert report)

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of triamcinolone hexacetonide are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

A suitable Environmental Risk Assessment is provided in accordance with the guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMA/SWP/4447/00).

Benzyl alcohol is an excipient in the proposed formulation. The quantity of benzyl alcohol in this formulation is within the recommended limits; further, benzyl alcohol is included in the reference product formulation. However, the intravenous administration of benzyl alcohol to neonates has resulted in mortalities and the SmPC stipulates that the product should not be given to premature babies and neonates. In view of the proposed indications of arthritis rheumatoides, traumatic arthritis, synovitis, bursitis, osteoarthritis and other sub-acute or chronic conditions, it is unlikely that this product will be administered to neonates. Therefore, from a non-clinical perspective, the quantity of benzyl alcohol in the finished product formulation is acceptable.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics and Pharmacodynamics

No new data have been submitted with this application and none are required. The application has been made based on a "biowaiver" justification. The applicant has provided a justification as discussed under general considerations fully supported by the pharmaceutical comparability of the proposed product and the reference product, which is considered adequate to support the biowaiver claim for this application especially as:

- Triamcinolone hexacetonide is clinically well-established and the proposed posology is broad (2 – 20 mg based on joint size and amount of articular fluid). The proposed therapeutic index of triamcinolone hexacetonide is broad
- The onset of action can take more than 24 hours and the duration of action lasts for a longer duration (4-6 weeks)
- The mean residence time after intra-articular injection is about 6 days
- The systemic exposure is slow and generally low, and therefore systemic risks are low. This is a property of the active substance and not the formulation
- The adverse events of significance like infections, inaccurate injections, in patients is related more to the procedure than the medicinal product

The MHRA is satisfied with respect to the pharmaceutical equivalence of this product and its reference product, based on careful consideration of bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.) which makes no specific reference to parenteral locally acting suspension products, but makes allowance for intra-

venously administered bi-phasic emulsions to be considered on a case-by-case basis.

Efficacy

No new data on efficacy have been submitted and none are required for this application.

Safety

No new safety data were submitted and none were required for this application

SmPC, PIL and Labels

The SmPC, PIL and labels are acceptable from a clinical perspective.

Pharmacovigilance System and Risk Management Plan

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A risk management plan has been developed to ensure that the product is used as safely as possible. Based on this plan, safety information has been included in the approved Summary of Product Characteristics and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of a Marketing Authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY**

The important quality characteristics of Triamcinolone Hexacetonide 20 mg/ml suspension for injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for this application.

CLINICAL

No new clinical data have been submitted with this application and none are required. The application has been made based on a "biowaiver" justification.

The MHRA is satisfied with respect to the pharmaceutical equivalence of this product and its reference product, based on careful consideration of bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.) which is silent to parenteral locally acting suspension products, but makes allowance for intra-venously administered bi-phasic emulsions to be considered on a case-by-case basis.

The evidence provided is considered adequate to support the grant of a marketing authorisation for Triamcinolone Hexacetonide 20 mg/ml suspension for injection with the same indications as those for the reference product Lederspan 20 mg/ml suspension for injection. In addition, suitable literature reviews have been submitted for the approval of the additional indication of juvenile idiopathic arthritis (JIA).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and text versions of labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Triamcinolone Hexacetonide 20 mg/ml suspension for injection has shown to be similar to the reference product Lederspan 20 mg/ml suspension for injection based on comprehensive analysis of pharmaceutical attributes. Therefore, the efficacy and safety profile of Triamcinolone Hexacetonide 20 mg/ml suspension for injection and the reference product Lederspan 20 mg/ml suspension for injection is expected to be the same. Extensive clinical experience with triamcinolone hexacetonide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome