

A.37 (item number)	Triamcinolone hexacetonide - Juvenile idiopathic arthritis (application title)	
Does the application adequately address the issue of the public health need for the medicine?	<div> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable </div> <p>Comments: <i>JIA is the most common chronic rheumatic disease of childhood, affecting approximately one per 1000 children.</i></p>	
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	<p><i>There are no other therapeutic agents for JIA and currently included in the Model List, excepting Acetylsalicylic acid* (acute or chronic use) which is listed for juvenile joint disease in general:</i></p> <ul style="list-style-type: none"> • <i>21st WHO Model List of Essential Medicines (2019) - pg 5, 29.3 Juvenile joint diseases - acetylsalicylic acid* (acute or chronic use).</i> • <i>7th WHO Model List of Essential Medicines for Children (2019) - pg 37, 29.3 Juvenile joint diseases - acetylsalicylic acid* (acute or chronic use).</i> <p><i>Considering other therapeutic agents available in the market:</i></p> <ul style="list-style-type: none"> • <i>Triamcinolone hexacetonide (TH) is strongly recommended over triamcinolone acetate (TA) for intraarticular glucocorticoid injections in JIA patients (moderate evidence certainty) due its longer effect duration and similar safety profile [Ringold 2019; Zulian 2004].</i> • <i>Intra-articular TH is supposed to present a better safety profile than oral corticosteroids, but this must be confirmed by comparative studies.</i> <p><i>The proposal is for TH to be added to the EML as TH has greater efficacy than TA. Based on supply issues, it is proposed that TH to be the listed medicine for intra-articular use and that TA, could be used where supply of TH is not available.</i></p>	
Have all important studies and all relevant evidence been included in the application?	<div> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable </div> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p> <p><i>A retrospective cohort, including 49 children (111 joints) with oligoarticular JIA showed that after 6 months, response rates were better for individuals injected with TH compared to TA (73% vs. 51%, $p = .016$). No difference in side effects between the two groups was noted. [Harhay 2021]</i></p>	

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<p>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).</p> <p><i>No study was presented comparing oral corticosteroids x intra-articular TH for any type of JIA.</i></p> <p><i>A double-blind trial included 37 children with at least 2 symmetrical joints requiring injection (86 joints) and one of the joints was injected with TH and the other with TA (equivalent dosing). All joints improved post injection; however between 2-21 months of follow up, 21 joints (53.8%) injected with TA relapsed in comparison with 6 (15.4%) joints in those who received TH. The rate of persisting or sustained response was higher with TH than with TA (at 6 months 89.7% vs 61.5% $p=0.008$, at 12 months 84.6% vs 48.7% $p=0.001$ and at 24 months 76.9% vs 38.5% $p=0.001$). There was no statistically significant difference in the rate of complications between the joint groups which was very low in both groups [Zulian 2004]</i></p> <p>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?</p> <p><i>Joint injections are contraindicated in the context of:</i></p> <ul style="list-style-type: none"> • <i>Active tuberculosis (systemic or local / intra-articular)</i> • <i>Systemic mycoses and parasitoses o Herpes simplex keratitis</i> • <i>Acute psychoses (due to the potential impact of systemic absorption of steroids)</i>
<p>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p><i>The overall benefit to risk ratio is highly uncertain because of the limited evidence both for efficacy and safety of TH in comparison with other therapeutic options for JIA.</i></p>

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Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	<i>The overall quality/certainty of evidence is unknown.</i>
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: skills on techniques of intra-articular injections are required for the physician and antiseptic and hygienic measures must be ensured as well.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: <i>no guideline was found.</i>
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	<p><i>There is limited data for comparative cost evaluation and cost-effectiveness of TH.</i></p> <p><i>The applicant stated that there are reported shortages of TH around the world and the manufacturers are working to address the supply issues and enable TH to be available on a more sustainable basis.</i></p> <p><i>The applicant presented cost estimate of TH in Australia where TH brand Lederlon is available via the Special Access Scheme (SAS) and costs Aus\$15.42 per 20mg/mL (2mL) vial (total of 40mg per vial).</i></p>
Any additional comments	---
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	<p><i>Considering that:</i></p> <ul style="list-style-type: none"> - <i>There is limited data for comparative efficacy and safety of TH versus oral corticosteroids or DMARDS for any type of JIA.</i> - <i>A risk of restrictive access was highlighted by the applicants and the cost in low-income countries was not presented.</i> - <i>skills on techniques of intra-articular injections are required</i> <p><i>The proposed recommendation to the Expert Committee is to not incorporate intra-articular TH on the EML and EMLc.</i></p>

<p>References (if required)</p>	<p><i>Bloom BJ, Alario AJ, Miller LC. Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. Rheumatol Int. 2011; 31:749–56. [PubMed: 20155422]</i></p> <p><i>Harhay R, Jeelani W, Agbor BTA, Hennon T, Wrotniak BH, Abdul-Aziz R. Response to treatment with intra-articular triamcinolone hexacetonide and triamcinolone acetone in oligo articular juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2021 Mar 20;19(1):36. doi: 10.1186/s12969-021-00520-6. PMID: 33743721; PMCID: PMC7981872.</i></p> <p><i>Lanni S, Bertamino M, Consolaro A, Pistorio A, Magni-Manzoni S, Galasso R, et al. Outcome and predicting factors of single and multiple intra-articular corticosteroid injections in children with juvenile idiopathic arthritis. Rheumatology (Oxford). 2011; 50:1627–34. [PubMed: 21561981].</i></p> <p><i>Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, Bohm M, Nieto-Gonzalez JC, Pistorio A, et al. Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken). 2013;65(7):1112-1120.</i></p> <p><i>Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, Colbert RA, Feldman BM, Ferguson PJ, Gewanter H, Guzman J, Horonjeff J, Nigrovic PA, Ombrello MJ, Passo MH, Stoll ML, Rabinovich CE, Schneider R, Halyabar O, Hays K, Shah AA, Sullivan N, Szymanski AM, Turgunbaev M, Turner A, Reston J. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken). 2019 Jun;71(6):717-734. doi: 10.1002/acr.23870. Epub 2019 Apr 25. PMID: 31021516; PMCID: PMC6561125.</i></p> <p><i>Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners P. Triamcinolone acetone and hexacetonide intra- articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double- blind trial. Rheumatology (Oxford) 2004;43:1288–91.</i></p>
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