WHO EML Application

Intra-articular corticosteroids (Triamcinolone Hexacetonide (□))

Condition Juvenile Idiopathic Arthritis

1	**Summary Statement of the proposal for inclusion.** **The application proposes the inclusion of triamcinolone (hexacetonide (□)) on the complementary list of the EML and EMLc for the treatment of Juvenile Idiopathic Arthritis (JIA).** **The rationale for the complementary list is that the use of this drug requires specialised care. The proposed listing on both the EML and EMLc reflects the fact that JIA affects children through adolescence and into adulthood. This rationale is consistent with the listing for the anti-TNF biologics currently listed for JIA.** **JIA is the most common chronic rheumatic disease of childhood, affecting approximately one per 1000 children (1). JIA is characterised by joint inflammation of more than 6 weeks' duration, with onset before age sixteen years and where no other cause is found (2). JIA is an autoimmune, non-infective, inflammatory joint disease, the cause of which remains poorly understood with both genetic and environmental contributions (3). JIA is a distinct entity from adult rheumatoid arthritis, differing in the clinical presentations, prognosis, disease outcomes and treatment approaches. The age of onset in JIA is typically young, with a peak incidence between 1-3 years of age (4), although the disease persists into adulthood in approximately 50% of cases. Even in patients in whom the inflammatory disease resolves, joint or extra-articular damage (such as eye inflammation called uveitis) – with associated disability – are common and if not treated then than can result in irreversible sequelae with significant impact on quality of life (5). A noteworthy complication of JIA is inflammatory uveitis. This affects up to 30% of children with JIA and – if undiagnosed and untreated – may cause irreversible loss of vision (6). There is considerable overlap between the medications used to treat JIA-arthritis and JIA-uveitis, namely immunosuppressive agents.** **Over recent decades the outcomes for children with JIA have improved substantially. In order to prevent joint destruction, chronic pain and disability, as well as extra-articular complications such as blindness from uveitis, the treatment paradigm for JIA has shifted: earlier, more aggressive therapy with early introduction of disease modifying therapy, and in many cases biological agents, is now the standard of care (7). The current treatment approaches for children with JIA aim for normal physical and psychosocial functioning, and with access to modern treatments, good outcomes are a realistic and achievable goal for many children with this condition (8).**

	The International League of Associations for Rheumatology (ILAR) recognizes 7 distinct subtypes of JIA; this classification is based primarily on the disease phenotype as well as demographic and serological factors (2, 9). The term JIA replaces former terms of Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA) and there are differences in the terminology based on disease presentation and classifications. This is important to bear in mind when reviewing the literature and clinical studies when different classifications were used. **This proposal focused on the medicine called Triamcinolone hexacetonide (TH) which is a long acting injectable corticosteroid. This medicine has for decades been routinely used for the treatment of inflammatory arthritis by paediatric rheumatologists. It is injected into the affected joint(s) and is considered as standard in the treatment of JIA, in particular in JIA subtypes where there are 1-4 joints affected (so called oligoarthritis / oligoarticular forms of JIA) and for joints which are technically amenable to joint injections (more details in section 7) (10).**
2	**Relevant WHO technical department and focal point.** **As far as we are aware there is no specific WHO technical department.**
3	**Name of organisation(s) consulted and/or supporting the application.** **Please see the attachments in the Appendix; Letter of introduction from the Paediatric Global Musculoskeletal Task Force and Letters of Support from many institutions and organisations from around the world.** **<u>International / National Organisations</u>** • **Paediatric Task Force for Global Musculoskeletal Health (members of the Task Force have worked together to submit this application)** • **Paediatric Rheumatology European Society** • **Australian and New Zealand Paediatric Rheumatology Group** • **South African Rheumatism and Arthritis Association** • **Paediatric Association for African League of Associations for Rheumatology** • **American College of Rheumatology** • **Childhood Arthritis and Rheumatology Research Alliance** • **Asia Pacific League of Associations for Rheumatology Paediatric Rheumatology Interest Group** **<u>Patient and Family Organisations</u>:** • **Arthritis Kids South Africa** • **European Network for Children with Arthritis** • **Juvenile Arthritis Foundation Australia** • **Versus Arthritis** **A recent online survey by the Paediatric Global Task Force for Musculoskeletal Health resulted**

	in 97 responses from key opinion leaders in 42 countries (mostly Africa and Asia) to determine the key medicines to treat JIA in their country and health care settings (Scott et al in press and included with the application as an Appendix); 86% respondents judged Intra-articular Triamcinolone Hexacetonide (TH) would be 'ideal' to be added to the WHO EML.
4	**International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.** **INN: Triamcinolone hexacetonide** **ATC: H02AB08** **INN: Triamcinolone acetonide** **ATC: H02AB08**
5	**Dose form(s) and strength(s) proposed for inclusion: including adult and age-appropriate paediatric dose forms/strengths (if appropriate).** **Triamcinolone hexacetonide for Intra-articular injection:** **20mg/mL in 2mL vial, 20mg/mL in 10mL vial.** **Triamcinolone acetonide for Intra-articular injection:** **10mg/mL in 1mL vial, 40mg/ml in 1mL vial.** **The above formulations and strengths are suitable for use in both paediatric and adult populations. Details about the treatment doses for children are provided below (section 7).**
6	**Whether listing is requested as an individual medicine or as representative of a pharmacological class.** **Triamcinolone hexacetonide (TH) is the glucocorticosteroid of choice for joint injections in JIA. TH is included in consensus guidelines of treatment in JIA (7) and has been demonstrated in clinical studies to be more efficacious (and longer acting) than Triamcinolone Acetonide (TA) as described further in section 9.** **Our proposal is therefore for TH to be added to the EML and we propose TH be listed with a restricted □ as TH has greater efficacy than TA. Based on supply issues (addressed in section 12), we would propose that TH to be the listed medicine for intra-articular use and that TA, could be used where supply of TH is not available. Other glucocorticoids are not included in this proposal as there is no evidence to support their inclusion for intra articular use**

7	**Treatment details (requirements for diagnosis, treatment and monitoring).** **JIA is a condition where chronic arthritis persists for more than 6 weeks in children younger than 16 (2). The diagnosis is based on clinical assessment and excluding other known causes for arthritis, such as infections or other autoimmune diseases. Treatment is based on the principle of targeted early therapy to achieve disease control with absence of inflammation to prevent damage in joints (7, 11-13).** **Intra-articular steroids are used as first line treatment in the oligoarticular forms of JIA (where fewer than four joints are involved) (7). Often these injections will reduce inflammation and result in good disease control in the affected joint(s) for many months and indeed often longer term for many years (14). However some children with oligoarticular forms of JIA may need repeat injections or be treated with Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate to bring optimal disease control (7). Multiple joint injections can also be used in other forms of JIA to induce rapid remission as 'bridging agents' whilst commencing DMARDs such as methotrexate, which can take several months to reach full effect. It is important to note that nonsteroidal inflammatory agents (NSAIDs) offer symptom relief (of pain and stiffness) but are not disease modifying or disease remitting; in all cases of JIA, treatment with NSAID alone is no longer recommended (7, 8, 12).** **The dosage regime for Triamcinolone hexacetonide (TH) intra-articular injections for JIA is 1 mg/kg for large joints (knees, hips, and shoulders) and 0.5 mg/kg for smaller joints (ankles, wrists, and elbows). For the hands and feet, 1-2 mg/joint for metacarpophalangeal/metatarso-phalangeal (MCP/MTP) joints, and 0.6-1 mg/joint for proximal interphalangeal (PIP) joints.** **Joint injections are uncomfortable and analgesia with local, inhaled (e.g. nitrous oxide) or general anaesthesia or sedation are recommended and especially if several joints are to be injected. Joint injection procedures must be carried out using aseptic technique and be performed by appropriately trained clinicians. Imaging (such as ultrasound or radiographic image intensifier) can be used to optimise the accuracy of needle placement – especially for small joints or 'deep' joints such as hip or subtalar joints (7, 15). Where trained paediatric rheumatologists are not available to undertake joint injection procedures, other trained clinicians can be involved in clinical care and perform joint injections, although it is strongly recommended that the management links with paediatric rheumatologists through clinical networks (7, 13, 16).** **JIA disease activity is monitored using standard assessment tools such as the Juvenile Arthritis Disease Activity Score (JADAS) (17), based on Active Joint Count, Patient/Parent Visual Analogue Scale (VAS) for health status and a Physician/health care provider VAS for disease activity. The JADAS may also include blood markers of inflammation (such as CRP and ESR). There are well defined 'cut offs' of the JADAS for low disease activity and remission which are the ultimate aim of therapy (17) – these 'cut offs' relate to joint swelling, joint stiffness, range of movement, pain, and return to normal activities / daily function (14). The literature also cites other measures of outcome which have been used in studies of JIA (reviewed in (17) and are described further in section 9). The early use of joint injections in oligoarticular JIA, which most commonly affects**

	the knee joint, have significantly reduced complications of untreated joint inflammation which includes joint damage, limb deformity, muscle wasting and difficulty in walking (18). **Only clinical personnel appropriately trained and experienced are to be involved in the use of this drug to treat active joint disease in JIA (7, 8, 12-14, 19) and this is the recommendation from international standards of care (7, 13, 16). Prior to joint injections, all patients with suspected JIA are recommended to be clinically reviewed by an experienced clinician to confirm the diagnosis of JIA and establish the treatment plan. Patients and their parents / carers need to have information and support to know when to seek health care attention (in the event of adverse event such as infection) or disease flare (13); this is often delivered by the multidisciplinary team. Patients will usually be reviewed 6-8 weeks after joint injection(s) and then subsequently (ideally every 3-4 months) to assess response to treatment and any adverse events (14).**
8	**Information supporting the public health relevance.** **Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of childhood, affecting approximately one per 1000 children (20). It is characterised by joint inflammation of more than 6 weeks' duration, with onset before age sixteen years and where no other cause is found (8, 9, 21). There are estimated to be more than 2 million children with JIA around the world and most of whom are in Africa and Asia (22); these estimates have been derived from known prevalence rates of JIA and modelling using population data for each country. Access to 'right care' remains a major problem for many children with JIA (23) likely with multifactorial explanation (24). Given the workforce shortages amongst paediatricians and especially in Asia and Africa (25), it is likely that many children with JIA have little or no access to specialist care and treatment and this is borne out with worse clinical outcomes in low resource income countries (26).** **The consequences of untreated JIA are known from historical studies that predate current approaches to treatment; essentially untreated arthritis results in pain, fatigue, joint damage, functional disability and impact on quality of life. The general effects of JIA include fatigue anaemia, poor growth and delayed puberty and many children can develop uveitis which results in blindness if not detected and treated (8, 9, 26). For untreated arthritis involving lower limb, this leads to difficulty in walking, getting up from sitting or a squat position and for upper limb joints this can result in difficulty in writing, dressing and feeding. For many children with untreated JIA, there are often absences from school with impact on peer interactions and long term studies demonstrate psychosocial impact, mental ill health issues and higher unemployment (27-29) compared to healthy peers. It is therefore very likely that the burden of untreated JIA is high and especially in low resource income settings where the true burden is likely under-recognised (16, 30).** **Current treatment approaches for children with JIA aim for normal physical and psychosocial functioning; with prompt access to modern treatments this is now an achievable goal for many children and joint damage, chronic pain and subsequent disability can be prevented with considerable improvement in quality of life (8, 13). This paradigm shift to earlier, more aggressive therapy with the early introduction of disease modifying therapy, including joint injections, is now the standard of care in high resource settings (7, 13). The situation is sadly not the same around the world where many children with JIA remain undiagnosed and**

	untreated with significant impact on the lives of the children themselves, their families and society as a whole. It is therefore more important than ever that the inequity in access to 'right care' is addressed; this is a priority for the paediatric rheumatology community (31); raising awareness (32), models of care and training to enable the existing workforce to make a diagnosis of JIA and deliver care, are the focus of many collaborative initiatives (31). The growth of paediatric rheumatology around the world is gaining momentum; having necessary medicines available through the WHO EML will be an important step to address the inequity and enable many children with JIA to be treated to avoid disability and have a better quality of life.
9	**Review of benefits: summary of evidence of comparative effectiveness.** **Search strategy: PubMed search of intra-articular steroid, paediatric, systemic, juvenile idiopathic arthritis.** **Intra-articular corticosteroids are recommended in treatment guidelines as first-line therapy for the oligoarticular forms of JIA (12, 19, 33). Triamcinolone hexacetonide (TH) and triamcinolone acetonide (TA) are the two most commonly used long-acting steroids for treatment of JIA. Key studies exist comparing TH and TA in children with inflammatory arthritis and these are described further below.** ***Please note: the nomenclature for inflammatory arthritis has changed over the decades and JIA is now the universally accepted term for chronic inflammatory arthritis in children as outlined in section 1. Furthermore the outcome measures used in clinical studies have also changed – we describe the outcomes in each published study, but it is noteworthy that it is not easy to compare historical studies. For the purpose of this section the term pauci-articular JRA (Juvenile Rheumatoid Arthritis) or JCA (Juvenile Chronic Arthritis) is equivalent to oligoarticular JIA (9, 14). Pauci-articular JCA can be further subdivided into Type I and Type II but are included and equivalent under the umbrella classification of JIA (9).*** **In 1986, Allen et al. conducted a study to evaluate the effect of steroid injections in children with pauciarticular JRA and other oligoarticular forms of inflammatory arthritis and who had failed therapy with non-steroidal anti-inflammatory drugs (NSAIDS) (34). Forty patients with active arthritis were recruited; 29 had pauciarticular JRA, 6 had psoriatic arthritis, 4 had seronegative enthesopathy arthropathy arthritis, and 1 had ankylosing spondylitis. The active joints were injected with 20-40 mg of TH (per active joint). A good response was defined as complete resolution (by clinical examination) of active joint inflammation (defined as joint effusion, heat and or tenderness of the affected joint). A relapse was defined as sustained re-accumulation of joint effusion, with or without heat or tenderness and determined following physician assessment. The study results included no immediate complications (such as infection), and all joints had a good response to the injection. Sixteen joints were noted to have limitation of range of motion but in all cases, improvement in range of motion was observed. In 50% of the joints of the children with JRA and in 30% of those with other forms of inflammatory arthritis, a good response was maintained for 12 months and there was no statistically significant difference based on disease group, sex, or drug dose. In 50% of the knees of the children with JRA and 30% of those with other types of arthritis, a good response was maintained for 12 months. There was no statistically significant difference based on disease group, sex, or drug**

dose. Eight joints relapsed and consequently were re-injected with TH; of these, 5 of the 8 maintained a good response following second injection. The mean drug dose in the pauciarticular JRA response group was 1.08 mg/kg; in the relapse group it was 0.65 mg/kg ($p<0.01$). In the patients with other types of juvenile arthritis, such as psoriatic arthritis, enthesopathy-arthropathy, and juvenile ankylosing spondylitis, the mean dose was 0.73 mg/kg in the good response group and 0.9 mg/kg in the relapse group (not significant). In summary, this study demonstrated that for children with pauciarticular JRA, intra-articular injection of TH result in rapid resolution of joint swelling with only one patient experiencing side effects of mild skin atrophy at the injection site.

In 2000, Breit et al reviewed all subgroups of JCA treated with either single or repeated TH injection 1989-1994(35). A total of 1439 TH injections were given to 194 patients, and 368 of these were re-injections. Efficacy and duration of the benefits were evaluated after a mean duration of 3, 15, 30, and 64 weeks. Responses significantly differed among subgroups ($p = 0.0001$): there were 121 weeks of efficacy in early-onset pauciarticular JCA type I, 47 weeks in late-onset pauciarticular JCA type II, 105 weeks in rheumatoid factor negative polyarticular JCA, 63 weeks in rheumatoid factor positive polyarticular JCA, and 36 weeks in systemic JCA. Side effects were reported as rare. The primary conclusion was that intra-articular TH is an effective therapy for inflammatory joint disease of all kinds of JCA.

In 2003, Zulian et al performed an open, prospective study on 85 patients with JIA (36). The study was not randomized, but patients were injected with either TH or TA depending on drug availability. The clinician assessing the response was blinded to the drug choice. One hundred and thirty joints of 85 patients were injected with either TH (70 joints) or TA (60 joints). The response rate was defined by core outcome measures defined using four variables to produce an articular score – these variables were joint swelling, limitation of joint range of motion, pain on passive movement, warmth to touch. A gradation severity score of 0-3 was assigned to each measure. A good response was defined as the absence of inflammation or as a decrease in joint inflammation leading to a reduction in the articular score of more than 60% from baseline. Relapse was defined as the reappearance of arthritis after a period of good response, defined as above. The rate of response was significantly higher with TH than with TA (81.4 vs 53.3% ($p=0.001$) at 6 months, 67.1 vs 43.3% at 12 months ($p=0.006$) and 60% vs 33.3% ($p=0.002$) at 24 months). The rate of relapse in the TA group was 2.7 times greater than in the TH group (95% CI 1.6–4.8). Only two patients in each group developed skin atrophy at the injection site.

In addition, a retrospective review by Eberhart et al, of 85 patients (227 joints) compared th effectiveness of TH to TA in JIA (10). Fifty-one patients (114 joints) received TH and 48 (113 joints) received TA. Concurrent medications were similar in the 2 treatment groups. On average, the relapse time in the TH group was longer than that of the TA group (10.36 ± 0.72 vs 8.45 ± 0.78 months). After adjusting for sex, duration of illness, or type of arthritis, the formulation of intra-articular injection (TH or TA) was still significantly different with respect to relapse time ($p < 0.0001$). The hazard ratio attributed to the injection type was 1.99 (95% CI 1.43, 2.78).

Zulian et al. conducted a double-blind trial comparing outcomes of 37 children who received an intra-articular steroid injection with TH (up to 1mg/kg/joint) or TA (up to 2mg/kg/joint) (37). Inclusion criteria were that children had at least 2 symmetrical joints requiring injection (i.e. 2 affected knees or 2 affected ankles). One of the joints was injected with TH and the other with

	TA (equivalent dosing) and 86 joints in total were injected. Children were reviewed before treatment and at 3, 6, 9, 12, 18, and 24 months post treatment. The response rate was defined by Core Outcome Measures defined using four variables to produce an articular score – these variables were joint swelling, limitation of joint range of motion, pain on passive movement, warmth to touch. A gradation severity score of 0-3 was assigned to each measure. 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 that 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). This is a key point, as sustained response from medication may overall be cost-effective, as children will require fewer injections if TH is used. There was no statistically significant difference in the rate of complications between the joint groups which was very low in both groups (37). **In summary, based on these studies, the evidence suggests that children with inflammatory arthritis had an effective response to TH and to a lesser extent TA. Those who received TH had a statistically significant lower rate of, and time to relapse than when compared to those injected with TA.** **To our knowledge there are no studies of other glucocorticoids for intra-articular use, but anecdotally other forms of glucocorticoid are not efficacious and are not to be recommended.**
10	## Review of harms and toxicity: summary of evidence of safety. **To our knowledge there is no published estimate of total patient exposure to TH or TA. However, most practicing paediatric rheumatologists will have 'in house' databases of patients under their care and record information about treatments and clinical progress ; this will likely include documentation of intra-articular steroids as they are one of the most commonly used treatments in paediatric rheumatology practice. However this data is not published or publicly available.** **TH is the least soluble glucocorticosteroid preparation; it has an alternative side chain which gives it much lower solubility than TA (38). TH has the least solubility profile and thus longer duration of action when used in joint injections. TH has no affinity for the mineralocorticoid receptor. The potential for glucocorticosteroid injections to be systemically absorbed is a risk, as they can cause adrenal suppression and/or iatrogenic Cushing syndrome. These adverse effects have been reported in single cases reports but are regarded as very rare (8); true prevalence is difficult to ascertain, but any effects are short-lived. Diabetic children may require a temporary increase in insulin doses (39, 40) following joint injections but again reports are rare and the effects are transient.** **Avascular necrosis (AVN) of the femoral head (at the hip joint) has been reported in historical (older) studies where patients were also taking oral systemic steroids. The prevalence of AVN has been reported as 0.024 in patients taking both systemic and intra-articular steroids; the incidence of AVN following intra-articular steroids alone has not been reported (41) but is likely**

	low. **The side effect / adverse event profiles of TH and TA are similar for each drug (7, 8, 37, 39, 40), as listed below, and the complications are regarded as uncommon. It is noteworthy that most side effects / adverse events can be greatly reduced with good clinical technique and accurate needle placement; hence the recommendations for joint injections to be performed by appropriately trained clinicians (7, 13).** o Infection (septic arthritis at the site of injection) is a theoretical risk for both drugs as they are glucocorticoid steroids, however reports are rare. o Subcutaneous atrophy caused by extravasation of the drug from joint space into surrounding tissues. This often resolves over time in most patients but can persists in some cases. o Steroid lipodystrophy is rare, but is more common over fingers, toes, wrists and ankles and subtalar joints where joint access is technically more difficult, or the joint space is limited. o Pain initially post injection (rare). o Calcium deposition in the joint (detected on radiographs but has no effect on joint function). o Treatment failure (i.e. failure to control inflammation). o Systemic absorption of glucocorticoids - rare as noted above. o Avascular necrosis (hip joint) as noted above. **Joint injections are contraindicated in the context of:** o Active tuberculosis (systemic or local / intra-articular) o Systemic mycoses and parasitoses o Herpes simplex keratitis o Acute psychoses (due to the potential impact of systemic absorption of steroids) **Caution should be exercised in the use of the medication in the following circumstances; this is more relevant to adult rheumatology practice but for completeness, we have included the comprehensive list.** o Injection should not be carried out in the presence of any active infection located near the affected joint o Cardiac insufficiency, acute coronary artery disease, Hypertension o Thrombophlebitis, thromboembolism o Myasthenia gravis, Cushing's syndrome, Diabetes mellitus, Hypothyroidism o Osteoporosis o Gastric ulcer, diverticulitis, ulcerative colitis, recent intestinal anastomosis o Exanthematous diseases o Renal insufficiency, acute glomerulonephritis, chronic nephritis o Cirrhosis o Infections that cannot be treated with antibiotics o Metastatic carcinoma o Due to the presence of Benzyl Alcohol as a preservative agent, TH should never be used in neonates or low birth-weight neonates. However it is noteworthy that a diagnosis of JIA in neonates is so rare that opinion from a paediatric rheumatologist would be imperative.
11	**Summary of available data on comparative cost and cost effectiveness of the medicine.**

	The dosage regime for Triamcinolone hexacetonide (TH) for intra-articular injections in JIA is 1 mg/kg for large joints (knees, hips, and shoulders) and 0.5 mg/kg for smaller joints (ankles, wrists, and elbows). For the hands and feet, 1-2 mg/joint for metacarpophalangeal/metatarso-phalangeal (MCP/MTP) joints, and 0.6-1 mg/joint for proximal interphalangeal (PIP) joints. The dosage regime for Triamcinolone acetonide is generally regarded as being double the dose for TH and is cited as such in the studies described in section 9. **Triamcinolone hexacetonide (TH) 20mg/mL vial is marketed under the trade name of Aristospan or Lederlon. The cost per vial is variable per country but as an example, in Australia, the 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).** **Triamcinolone acetonide (TA) 10mg/mL and 40mg/mL is marketed under the trade name of Kenacort-A 10 and Kenacort-A 40 respectively. The cost in Australia is $3.13 AUD per 10mg/mL ampoule and $12.9 AUD per 40mg/mL ampoule. Costing in New Zealand is $4.16 NZD per 10mg/mL ampoule and $10.22 NZD per 40mg/mL ampoule.** **The cost of treatment per child is dependent on the number of joints to be injected and size of each joint with larger joints requiring larger doses of TA compared to TH. The cost of treatment per patient is therefore highly variable and may vary country depending on the cost of the medicines and whether TH or TA are used. We provide an example of a possible costing (and using the costing in Australia):** **An 80kg child with JIA and has 4 active large joints for injection. Dose (1mg/kg per joint) and the total dose of TH therefore required is 320mg - 8 of the 20mg/mL (2mL per vial) vials therefore would be required at a cost of approximately $130 total for medication alone. Triamcinolone acetonide 40mg/mL, 1mL vials cost $12.9 in Australia. The dose required to be given is double that of TH (i.e. 2mg/kg per large joint). Therefore, an 80kg child requiring 4 large joints to be injected would equate to a total of 640mg of TA (16 vials) at a total cost of approximately $206 for TA alone.** **The data in one study (Zulian et al (34)), suggests that TH is more likely to give a more efficacious and more sustained response and may therefore be more cost effective. To our knowledge there are no studies of overall cost effectiveness of intra-articular steroids in JIA although the true 'cost' of untreated JIA is undoubtedly very high to patients, their families and society (42). The need for better cost effectiveness studies of treated versus untreated JIA has been highlighted (43).**
12	**Summary of regulatory status and market availability of the medicine.** **There are reported shortages of TH around the world. As far as we are aware and at the time of this submission, the manufacturers are working to address the supply issues and enable TH to be available on a more sustainable basis. We would hope that inclusion of TH in the EML would actually help to further leverage action to address the supply issues.**

	At the time of writing the Aristospan product for TH is currently listed as short in supply in the U.S and has been discontinued in the U.S market by the FDA but is able to be imported on an individual patient basis. TH is not approved for use in Australia by the Therapeutic Goods Administration (TGA) but can be accessed through the Special Access Scheme (SAS) from international manufacturers. Canada recently approved TH for inclusion in their public drug plan formularies. TH is approved for intra-articular use in the UK and is included in the British National Formulary. Austria, Czech Republic, Portugal, Slovenia, Spain, The Netherlands and the UK agreed to grant a Marketing Authorisation for TH 28/11/2013 although this was prior to supply issues. **TA Is currently registered for intra-articular administration by the TGA in Australia, the FDA in the United States and in New Zealand. It has marketing authorisation in Sweden, Switzerland and Canada.** **In our submission to the WHO, we would propose that TA be included as an alternative medicine for intra-articular use in the absence of TH being available. We would not however recommend other glucocorticosteroids for intra-articular use.**
13	**Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).** **Triamcinolone Hexacetonide (TH) and Triamcinolone Acetonide (TA) are listed in the British Pharmacopoeia.**
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