Bijlage 4: Literatuuranalyse

Het literatuuronderzoek is verricht door het Kinderformularium.

Deze risico analyses zijn bijgevoegd als achtergrond informatie en niet ter beoordeling. De doseeradviezen zijn reeds beoordeeld en vastgesteld door de multidisciplinaire redactie van het Kinderformularium aangevuld met de werkgroep van de NVDV.

Inhoudsopgave

Kinderformularium: ciclosporin

Date literature search: 05-2020 Saved in Pubmed? ☒

Starting point (month-year): 05-2020

1. National registration/guidelines

AD: atopic dermatitis; CBC: complete blood count; CE: constitutional eczema; CsA: ciclosporin; Cr: creatinine; diff: differential; DLQI: dermatology quality of life index; EASI: Eczema area and intensity index; HCG: human chorionic gonadotropin; HIV; human immunodeficiency virus; IGA: investigator global assessment; K^+: potassium; Mg^+: magnesium; NRS: numeric rating scale; POEM: patient oriented eczema measure; TB: tuberculosis.

Source	Evidence	Effect	Remarks
Ref. 1a Neoral drank 100 mg/ml 16-09-2019 Ciqorin capsules 7-9-2018	SmPC	**4.2** In verscheidene studies hadden pediatrische patiënten vanaf 1 jaar hogere doses per kg lichaamsgewicht nodig dan volwassenen en verdroegen ze die ook. Het gebruik van Neoral bij kinderen voor niet-transplantatie indicaties anders dan nefrotisch syndroom kan niet worden aanbevolen. Behalve bij kinderen met nefrotisch syndroom, mag de totale dagelijkse dosis nooit 5 mg/kg overschrijden. **4.4** <u>Bijkomende voorzorgen bij atopische dermatitis</u> Stopzetten bij: - Therapieresistente hypertensie - Ernstige actieve herpes simplex infectie Let op bij: -Lymfadenopathie -Huidinfectie met Staphylococcus aureus De ervaring met het gebruik van Neoral bij kinderen met atopische dermatitis is beperkt. In klinische studies werden kinderen vanaf 1 jaar geïncludeerd. Het veiligheidsprofiel bij een standaard ciclosporinedosering was vergelijkbaar met het veiligheidsprofiel bij volwassenen. **5.2** Farmacokinetische gegevens van pediatrische patiënten aan wie Sandimmune of Neoral is toegediend zijn erg beperkt. Bij 15 niertransplantatiepatiënten (3-16 jaar), was de ciclosporinevolbloedklaring na intraveneuze toediening van Sandimmune 10,6±3,7 ml/min/kg. In een studie bij 7 niertransplantatiepatiënten (2-16 jaar) varieerde de ciclosporineklaring van 9,8-15,5 ml/min/kg. Bij 9 levertransplantatiepatiënten (0,6- 5,6 jaar) was de klaring 9,3±5,4 ml/min/kg. De verschillen in biologische beschikbaarheid tussen Neoral en Sandimmune bij pediatrische patiënten zijn vergelijkbaar met deze waargenomen bij volwassenen.	CsA voor atopische dermatitis bij volwassenen: 2,5-5 mg/kg/dag. In zeer ernstige gevallen starten > 5 mg/kg/dag; bij goede respons weer afbouwen. Een behandelduur van 8 weken kan genoeg zijn, maar 1 jaar is doeltreffend en wordt goed verdragen (mits controlerichtlijnen worden gevolgd) Neoral bevat ongeveer 12% vol. ethanol. Een dosis van 500 mg Neoral bevat 500 mg ethanol dat overeenkomt met bijna 15 ml bier of 5 ml wijn. Er moet rekening mee worden gehouden wanneer Neoral wordt toegediend aan een kind.

National guidelines		
Richtlijn constitutioneel eczeem (NVDV 2019)	Ciclosporine-A CE die niet voldoende reageert op lokale therapie: *>2 jaar:* Eventuele dosisaanpassing vindt plaats op geleide van klinisch effect of bijwerkingenprofiel. Monitoring van bloedspiegels wordt niet geadviseerd. Tijdens het gebruik van CsA dienen regelmatig controles plaats te vinden van bloeddruk en laboratoriumwaarden in verband met toenemende kans op bijwerkingen, zoals verminderde nierfunctie, hypertensie of huidmaligniteiten. CsA is een alternatief voor langdurige behandeling (>1 jaar). Monitoring: -Huidinspectie (IGA en controle cutane maligniteit) en jeuk (NRS). Aanvullend kunnen EASI, POEM en DLQI gebruikt worden. - Bloeddruk: meting herhalen. Bij blijvende bloeddrukstijging: dosisreductie of toevoeging antihypertensivum. - Creatininestijging > 130% tov uitgangswaarde: meting herhalen binnen 2 weken. Bij wederom stijging >130%: dosisreductie (25-50%). Geen daling creatinine: behandeling staken. - Bespreek interactie met NSAID's, levende vaccins, vermijden zonexpositie en grotere kans huidinfecties. - Bloedcontroles: **Tabel 8.** Monitoringsschema behandeling met CsA bij CE | Parameter	Bij intake	Periode in weken			Tijdens onderhoudsdosering (elke 3-6 mnd)	1x per jaar
---	---	---	---	---	---	---
		afh. van start dosering 4	8	12		
IGA en NRS jeuk*	x	x	x	x	x	
Bloeddruk	x	x	x	x	x	
Bloedonderzoek						
Hb, leukocyten, trombocyten	x			x	x	
leukocyten differentiatie	x			x	x	
ALAT, γ-GT, bilirubine	x			x	x	
serum creatinine	x	x	x	x	x	
Cholesterol en triglyceriden	x	x				x
Kalium**, urinezuur**	x					
Urinesediment**	x					
HIV§	x					
HBV/HCV§	x					
Zwangerschap§	x					
Grenswaarden: Leukocyten <3,0 x 10^9/L; Trombocyten <100 x 10^12/L; ALAT >2x de bovengrens van normaalwaarde → en overleg/verwijzen MDL arts; Bij stijging van serum creatinine > 130% boven de uitgangswaarde van de patiënt, dient de frequentie van controles geïntensiveerd te worden en evt. de dosering aangepast te worden.						| * Aanvullend kunnen de EASI, POEM of DLQI gebruikt worden. ** Standaard bij intake. Verdere monitoring op indicatie. § Uitsluiten (anamnestisch of testen) Op indicatie: Magnesium (bij spierkrampen) NB. Ciclosporine kan zo nodig veilig gegeven worden in de zwangerschap, i.o.m./ onder begeleiding gynaecoloog/kinderarts	Dosering (kinderen) De aanbevolen dosering van ciclosporine bij kinderen is te vinden via het **kinderformularium**. CsA dient voorgeschreven te worden door een specialist in kinderdermatologie. De dosis dient individueel vastgesteld te worden en de laagst mogelijke dosis dient toegepast te worden. Het advies is gebaseerd op Harper, Bemanian, El-Khalawany, Berth-Jones, Garrido Colmenero, Sibbald en Hernandez-Martin.
International guidelines		
Guideline	**Guidelines of care for the management of atopic dermatitis. Section 3.** (Sidbury et al. 2014) Summary (Harper 2000) CsA is an effective treatment for AD in the pediatric population, similar to adults. Both continuous long-term (up to twelve months) and intermittent short-term dosing schemes (three or six month courses) are efficacious. While continuous dosing is associated with better efficacy and longer sustained effects relative to	Indication: refractory AD Dosage: 3-6 mg/kg/day.

	intermittent use, dosing regimens should be determined on an individual basis.43 As with adult patients, the lowest effective dose to achieve the desired results should be given. Monitoring (in general): At baseline: BP (2 measurements), renal function, urinalysis with micro, fasting lipid profile, CBC/diff/ platelets, liver function, magnesium, potassium, uric acid, TB testing, HIV if indicated, HCG if indicated. Follow-up: BP every visit, renal function, liver function, lipids, CBC/diff/platelets, Mg^+, K^+, uric acid. If dose increased, check labs 2-4 weeks after. HCG if indicated, annual TB testing. If Cr increases > 25% above baseline, reduce dose by 1 mg/kg/day for 2-4 weeks and recheck. Stop CsA if Cr remains > 25% above baseline; hold a lower doses if level is within 25% of baseline. CsA trough level only if clinical response is inadequate or with concomitant use interacting medications.	
Guideline	**Guidelines of care for the management of atopic dermatitis. Part II.** (Wollenberg et al. 2018) <u>Summary</u> (Harper 2000). • CsA may be used (off label) in children and adolescent patients showing a refractory or severe course of disease. A detailed patient monitoring, especially of the renal status, is advisable. • Cessation of therapy or switch to another systemic drug should be attempted after 2 years of therapy, although many patients tolerate much longer therapy with lowdose CsA. • Since an intermittent-dosage regimen (e.g. 'weekend therapy') will lead to lower cumulative doses of CsA and is effective in some AE patients, an individualized dosage regimen is recommended for underage patients. • Although there are no controlled studies available regarding the efficacy of vaccination during CsA therapy, there is no evidence for a failure during cyclosporine either. Hence, a cessation of therapy of 2 weeks before and 4–6 weeks after vaccination may be advisable. Clinically, there is no evidence for this recommendation.	Starting dose children: 5 mg/kg/day Maintenance dose children: 2.5-3 mg/kg/day

2. Kinetics

- Plasma protein binding: ~90% (IM)
- Metabolism: Mainly metabolized by CYP3A4 to ~15 inactive metabolites.
- Excretion: Oral dose: ~6% is renally excreted, 0,1% as CsA. Main elimination is biliary.
- TDM (NVZA): Only TDM in unusual drug response for indications other than transplantation (IM). Toxicity > 400 µg/L.

3. Atopic dermatitis

Articles regarding oral use of CsA in severe, refractory AD in paediatric patients are summarized in the table below. The search was limited to studies that analysed the results of children separately. Case reports in the ages 2-18 years were excluded. All studies are observational unless stated otherwise. Green labelled studies were included in the monograph.

Study	Age	Dose (kg/day)	Dura-tion	Follo w-up	Outcome	Relapse	Disease-free period
(Guarneri et al. 1994), N=1 Case	15 mo	Mo 1: 3 mg Mo 2: 2 mg Mo 3: 1 mg	3 mo	6 mo	Significant improvement clinical features at 3 mo Complete remission of itching	Some in the next 6 mo	-
(Berth-Jones et al. 1996) N=27 Prospective	Mean 9 y (2-16 y)	5 mg (in 2 doses)	6 wks	10 mo	22/27 children complete clearing or marked improvement after 6 weeks. One child without improvement responded to Neoral later on.	17/20 pt (other 7 pt n/a)	6 mo (3 pt) 4 wk (6 pt) 2 wk (11 pt)
(Zaki, Emerson, and Allen 1996) N=18 Prospective	Mean 8.1 y (3-16 y)	5-6 mg	4-12 wks	Max 8 mo	16/18 children good to excellent In some children dose was reduced based on clinical response (not specified).	16/18 pt	Up to 6 mo in 2 pts
(Gonzalez-Otero, Donelli, and Saenz 1997), N=15 Prospective	Mean 7.4 y (4-14 y)	3-3.5 mg (in 2 doses)	1-3 mo	-	Excellent therapeutic response Treatment extended from 1 mo to 3 mo in 5 children	Some in the next 15 mo	-
(Harper et al. 2000) N=43 Unblinded RCT 1. Short course therapy (n=21) 2. Continuous therapy (n=19)	Mean 10.1 y (2-16 y)	5 mg, reduction after 4 wk and max 25% per month thereafter (1) or dose tapering in week 8-12 (2)	12 wks (1) or 1 y (2)	12 mo	30/40 children significant improvement in severity, area, pruritus, irritability and sleep disturbance at week 8, week 12 and 12 months in both treatment arms. Mean dose at month 12 was 3.2 mg/kg/day (1) and 2.7 mg/ kg/day (2). Mean cumulative dose was higher in the continuous arm (1068 ng/kg vs 836 mg/kg in the short course arm).	12/19 pt (3 pt after 1 short course), 13/16 pt (2)	Up to 9 mo in 3 pts. Mean re-mission af-ter 1 short course:126 days(n=10)
(Bunikowski et al. 2001) N=10 Prospective	2-15 y	2.5 mg (in 2 doses), dose ↑ in week 2, 4 and 6 if SCORAD index reduction < 35% to max of 5 mg	8 wks	3 mo	Decrease of 50% of affected body surface in 9/10 pt after 9 wks. Maintenance dose was 2.5 mg/kg/day in 4 patients, 3.5 mg/kg/day in 4 patients, 4.5 mg/kg/day in 1 patient and 5 mg/kg/day in 1 patient. Dose escalation was mainly caused by a higher itching score.	7/9 pt	4 wks
(Bemanian et al. 2005) N=8 Unblinded RCT	Median 11.9 y	4 mg	3 mo	-	Mean SCORAD: 80 (day 1) → 35 (day 15) → 25 (day 90) → 25.02 (12 wks) → 21.01 (24 wks). All side effects disappeared with discontinuing medication.	-	-

(Haw, Shin, and Haw 2010) N=13 retrospective	Mean 10.8 y (5-14 y)	Mean 2.7 mg	Mean 13.5 mo (± 8.4)	-	Mean SCORAD: 30.0 ± 14.1 at baseline → 23.3 ± 10.1 (mo 1) → 15.8 ± 11.4 (mo 2) → 14.8 ± 9.3 (mo 4) → 13.4 ± 11.2 (mo 6). At each timepoint SCORAD was significantly improved from baseline. Dose reduction of 50 mg/4 wks according to therapeutic response. Discontinuation CsA when objective SCORAD ≤ 5.	13/13 pt	Mean 4.5 mo (± 2.9)
(Beaumont and Arkwright 2012) N=35	At init-iation: median 6 y (3-10)	5 mg (in divided doses), ↓ 1 mg/month if possible	Median 20 wks, (10-32)	-	17/35 pts had complete clearing or major clinical improvement (67-99% reduction in SCORAD) The time to initial response was 2 (66%) -4 weeks (100%).	2 pts re-started on CsA. Relapse rate unknown	-
(El-Khalawany et al. 2013) N=20 Unblinded RCT	Mean 10.3 y (7-14 y)	2.5 mg (in 2 doses)	12 wks	24 wks	Mean absolute reduction in SCORAD: 10.55 (4 wks) → 16.90 (8 wks) → 25.02 (12 wks) → 21.01 (24 wks). The time to initial response was 2-3 weeks, but the relapse after discontinuation was also short (both rapid compared to MTX)	Not de-scribed	Mean 2 wks
(Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015) N=5 Retrospective	Mean 12 y (10-14 y)	5 mg on Saturdays and Sundays (previous treatment: 5 mg/kg/day > 1 y)	20 wks (contin ued after study)	20 wks	4 pts maintained response (SCORAD score ≤ 30) with weekend therapy. 1 pt had to be restarted on daily CsA therapy. Authors note CsA is widely distributed in adipose tissue because of the high lipophility in the microemulsion formulation.	1/5 pts	-
(Sibbald et al. 2015) N=15 Retrospective	5-15 y	Mean initial dose 2.8 mg In responders without relapse: mean 3.0 mg (2-4)	Mean 10.9 mo ± 2.7 mo	Min 15 mo	12 of 15 patients had improvement in surface area, intensity and symptoms of disease. The 3 non-responders were older (13-15 y); 1 pt had poor adherence. For patients without relapse > 15 mo, the mean treatment duration tended to be longer (17.7 ± 10.7 vs. 10.2 mo ± 2.7). Tapering off was slower in patients that did not relapse (43% tapering vs. 60%).	5/12 pt (within 2, 5, 6, 8 and 12 mo)	Min 15 mo in 7 pts
(Hernandez-Martin et al. 2017) N=63 retrospective	Mean 8.4 y (± 3.6)	Mean initial dose 4.2 mg In responders 4.4 mg	median 4.6 mo (1.5-21.6)	Up to 21 mo	40/63 pt good/excellent response after 4 wks. Pts with poor outcome at 4 wks did not improve if therapy was continued. Absence of blood eosinophilia at baseline (80% of the patients) and egg allergy (56%) was associated with a better treatment outcome. The appearance of side effects was significantly associated with a longer time of treatment. CsA was tapered in 45 pts and stopped in 11 pts.	21/40 pts (most within 3 mo)	Up to 6 mo in 9 pts
(Saricaoglu et al. 2018) N=43 Retrospective	Mean 10.9 y (6-17 y)	Mean initial dose: 3.26 mg (2,5 – 5 mg)	4.9 mo ± 4.24	-	17/43 pts were good responder, 12/43 pts moderate responder and 14/43 were non-responders. No difference between groups in dose or other criteria, only in treatment duration (good: 7.44 mo, moderate 4.33 mo and poor 2.64 mo) CsA was tapered by 0.5-1 mg/kg daily every 2-4 weeks according to therapeutic response.	4/17 good respon-ders	-
(Yee and Orchard 2018) N=54	Mean 9.3 y (2-18 y)	5 mg (in 2 doses). Reduction to 1 mg	Mean 313 d	Unkn own	-	-	-

retrospective		with good clinical response	(4 d – 37 mo)	Total: 15 y			

CsA: ciclosporin; MTX: methotrexate; SCORAD: SCORing Atopic Dermatitis

Discussion:

Age limits

A 15 month old child was successfully treated with CsA for 3 months. (Guarneri et al. 1994)

PROPOSAL: adjust current lower limit for the age from 2 year old to 1 year old.
MEETING 10-9-2020: approved.

Treatment duration

Treatment duration has a great variation and depends on the study duration. If a range of treatment duration was provided, it was not always clear if shorter treatment durations were patients with insufficient response. One study provides treatment duration per group of responders: 2.6 mo for poor responders, 4.3 months for moderate responders and 7.4 months for good responders. (Saricaoglu et al. 2018) In the older studies (< 2001) treatment durations of less than 2 months were investigated. After 2001 treatment was at least 3 months and in retrospective studies usually much longer (up to 37 months (Yee and Orchard 2018)). In one study 5 patients who used CsA 5 mg/kg/day for more than 1 year continued treatment in a weekend therapy regime. For 4 patients this was sufficient and they continued weekend therapy after the study ended at 20 weeks. (Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015) One study concludes that a longer treatment duration tends to decrease the risk to relapse. A more gentle tapering of the dose also tends to prevent relapse. (Sibbald et al. 2015)
On the other hand, Harper shows that some patients were able to stay in remission for at least 9 months after just 12 weeks of treatment with an initial dose of 5 mg/kg/day. (Harper et al. 2000) The high initial dose does not explain the success of treatment: Sibbald has a low mean dose of 2.8 mg/kg/day (3 mg/kg/day for non-relapsing responders), comparable age groups and a longer follow-up. (Sibbald et al. 2015)
In the trial protocol for the RCT TREAT (comparing MTX and CsA for atopic dermatitis in children) CsA is used for 36 weeks with a follow up period of 24 weeks after cessation. (Irvine et al. 2018)

PROPOSAL: an optimal or maximum treatment duration cannot be provided: some patients do well on just 12 weeks of treatment while others still relapse after 13.5 months of treatment (or longer). Based on Garrido treatment > 1 year should be an option. The next sentence can be added after 'maintenance dose': gedurende tenminste 3 maanden. Een behandelduur van meer dan een jaar is ook beschreven.
MEETING 10-9-2020: rephrase to 'If no improvement occurs within 4 weeks with the highest dose tolerated, discontinuation of ciclosporin should be considered. Duration of treatment if efficacy established at least 3 months.'

Initial dose

Most studies have a high initial dose and reduce dose based on clinical response. One study had a opposite titration schedule: the initial dose was 2.5 mg/kg/day and the dose increased if the therapeutic response was insufficient. (Bunikowski et al. 2001) Most patients remained at 2.5 mg-3.5 mg/kg/day,

but 7 out of 9 patients relapsed within 4 weeks after treatment. In the studies with relatively low relapse rates (Guarneri, Gonzalez, Garrido, Sibbald, Hernandez-Martin and Saricaoglu) initial doses between 2-5 mg/kg/day were used, although the mean doses in responders were around 3-5 mg/kg/day.

PROPOSAL: adjust current initial dose of 5 mg/kg/day to 3-5 mg/kg/day (in 2 doses).
MEETING 10-9-2020: approved.

Duration of initial dose
The current NKFK dose recommendation for Constitutional eczema mentions the initial dose should be used for 3 to 6 weeks (based on the guideline Constitutional Eczema from 2014). The 2019 guideline CE provides no specific recommendation for children, but states treatments of 6-12 weeks as crisis intervention are common in daily practice. (NVDV 2019) It is not clear if the high initial dose should be used all this time. But it does indicate the 3-6 weeks currently mentioned are no longer applicable. The literature does not provide an alternative period for the initial dose since this varies between 4 weeks until > 1 year. (Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015)

PROPOSAL: remove the current recommendation to use the initial dose for 3-6 weeks.
MEETING 10-9-2020: do not remove this

Maintenance dose
Most studies do not make a clear distinction between maintenance dose and initial dose: they present one mean dose for the duration of the therapy. In two unblinded RCT's one set dose was used (4 mg/kg/day and 2.5 mg/kg/day). (Bemanian et al. 2005, El-Khalawany et al. 2013) Another unblinded RCT used a monthly reduction of 25% after an initial dose of 5 mg/kg/day for 4 weeks. (Harper et al. 2000) In retrospective studies a decrease around 1 mg/kg/day per month is common. (Guarneri et al. 1994, Beaumont and Arkwright 2012, Haw, Shin, and Haw 2010, Saricaoglu et al. 2018, Yee and Orchard 2018) Other studies mention dose tapering, but do not specify how. (Hernandez-Martin et al. 2017, Sibbald et al. 2015, Zaki, Emerson, and Allen 1996)

Mean doses provided in retrospective studies range from 2.7 to 4.4 mg/kg/day. In one study 4 patients could remain treated with the initial dose of 2.5 mg/kg/day. (Bunikowski et al. 2001) One study examining CsA vs CsA + glucosamine described a > 50% reduced SCORAD in 15 out of 16 patients after 8 weeks of just 2 mg/kg/day CsA. (Jin et al. 2015) In the protocol for TREAT the used dose is 4 mg/kg/day. After 12 weeks, dose adjustments are permitted (increase to 5 mg/kg/day or unspecified decrease dependent on treatment response). (Irvine et al. 2018)
Another option is 'weekend therapy': 5 long term users of CsA (>1 year of 5 mg/kg/day) switched to 5 mg/kg/day every Saturday and Sunday. 4 out of 5 patients remained stable (blood levels of CsA decreased 21.7-25.3 ng/mL instead of 57.1-116.5 ng/mL with continuous therapy). (Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015)

PROPOSAL: adjust current maintenance dose of 2.5-3 mg/kg/day to 2-5 mg/kg/day (in 2 doses). If long term treatment with high doses is needed, weekend therapy can be considered. Gradual decrease of the maintenance dose is recommended.
MEETING 10-9-2020: weekend therapy is rephrased to after 1 year or more of daily use, 2 consecutive days per week followed by a 5-day break may be considered

Evaluation time

Time to initial response is only described in 2 studies and was 2-4 weeks. (Beaumont and Arkwright 2012, El-Khalawany et al. 2013) In the other studies this depended on the timepoints of the assessments. One study mentions that patients with poor outcome at 4 weeks did not improve if therapy was extended. (Hernandez-Martin et al. 2017)

QUESTION: should we keep 4 weeks as a timepoint to decide whether therapy should be continued or keep an extra margin of fe. 2 weeks? So evaluation after 6 weeks?

PROPOSAL: evaluation after 4 weeks: if no response, discontinue therapy.

MEETING 10-9-2020: approved.

Neoral vs generics

The older studies use ciclosporin capsules without a micro-emulsion, while newer studies all use Neoral. It is unclear whether the generics are also a micro-emulsion. Some studies state the effect of the micro-emulsion is faster and more sustained because of the high lipophilicity (Gonzalez-Otero, Donelli, and Saenz 1997, Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015) and one reported a patient that did not respond to traditional capsules, but did respond to Neoral later on. (Berth-Jones et al. 1996) Ciclosporin Aurobindo and PCH (capsules 25 mg and 100 mg) do not contain ethanol, Neoral, Ciquorin and ciclosporin Sandoz do contain ethanol. In the Netherlands Neoral is the only available oral solution.

QUESTION: should there be information included in the monograph about potential advantages and disadvantages of Neoral?

MEETING 10-9-2020: *Not discussed.*

4. Atopic dermatitis - monitoring

The articles in table 1 are also checked for information about monitoring of laboratory values and blood pressure. If the article provides specific recommendations, this is provided in the discussion.

Study	Excl criteria related to monitoring	Monitoring	Frequency of monitoring	Participants with lab abnormalities or high BP	Treatment alterations	Side effects in general
(Guarneri et al. 1994) N=1	-	FBC, LFT, renal function, UEC, IgE levels, CD4:CD8 ratio	Every 15th day	0	-	No side effects described
(Berth-Jones et al. 1996) N=27	High BP, abnormal renal function, hepatic function or complete blood cell count	BP, serum Cr, LFT, FBC	At screening and after 6 wks	0 (clinically relevant)	-	24/26 pt: good/very good tolerability
(Zaki, Emerson, and Allen 1996) N=18	None	BP, serum Cr, LFT	Every 2 wks	1 pt with serum Cr ↑ of 46%.	No alteration	Mild

(Yee and Orchard 2018) n=54	-	BP, FBC, UEC, LFT, magnesium, lipids and CsA level (< 1000 ng/ml, 2 h post-dose)	At screening, after 1 mo and every 3 mo. Also after dose increase and if Cr rose > 30%	9 pt: lymphophenia, elevated hepatic transaminase, neu-tropenia, hypertriglyceridemia and CsA level. 4 pt with Cr ↑ > 30%	2 pt terminated treatment due to hypertriglyceridemia. Others returned to normal without alterations.	7 pt with clinical side effects. 4 pt terminated treatment (nausea, lethargy, gum hypertrophy)
(Harper et al. 2000) N=43	abnormal renal or liver function and hypertension.	BP, biochemistry and hematology profiles	Not described (figures indicate monthly and 2 wks after start)	3 pt with Cr ↑ > 30%. 1 pt with Cr ↑ > 50%. None developed hypertension.	Serum creatinine returned to an acceptable level spontaneously or after dose reduction.	57% mild, 37% moderate, 6% severe
(Bunikowski et al. 2001) N=10	Cr (>10% ULN), uric acid (>20% ULN), bili-rubin (>50% ULN), alkaline phosphatase (>100% ULN), hepa-tic transaminases (>100% ULN); hyper-kalemia; hypertension	BP, FBC, UEC, LFT	Not described (probably every 2 wks)	1 pt with Cr ↑ > 30% Mean serum bilirubin ↑ (10.3 to 12.8 umol/l). All other values (incl BP) did not change or remained within normal range.	Serum creatinine returned to an acceptable level spontaneously Bilirubin follow-up is not described.	9/10 pt: good/ excellent tolerability
(Beaumont and Arkwright 2012) N=35	-	BP, FBC, UEC	Monthly	None Median max CsA through level: 47 µg/l (2 chld with through level > 100 µg/l).	-	Not specified. One pt with eczema herpeticum.
(El-Khalawany et al. 2013) N=20	none	FBC, UEC, LFT, ESR, BSL, IgE, hep B and C antibodies, chest X-ray and TB	At initiation, 4 wks, 8 wks, 12 wks and at the end of follow-up	2 pt with abnormal LFT 3 pt with abnormal renal function	None All adverse effects disappeared at the end of the follow-up period.	common side-effects: fatigue (45%), leuko-penia (35%), headache (25%), anemia (20%), flu-like symptom (20%)
(Sibbald et al. 2015) N=15	-	-	-	1 pt with high K^+ and se-rum Cr (2 mo after start) None developed hypertension.	Dose reduction and discontinuation after 15 mo	6 pt with clinical side effects. 4 pt terminated treatment
(Hernandez-Martin et al. 2017) N=63	Kidney or liver disease, high BP	BP, FBC, serum urea, CR, magne-sium, uric acid, bilirubin, lipids, urine osmolarity	Not described	2 pts with mild hyposthenuria (318 mOsm/kg) and urea increase (59 mmol/L).	Treatment was terminated	Mild. All side effects resolved within one month after CsA withdrawal.
(Saricaoglu et al. 2018) N=43	-	UEC, LFT and FBC	-	0	-	5 pts had mild/moderate side-effects
(Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015) N=5	-	BP, Cr	-	CsA blood levels Continuous: 57.1-116.5 ng/mL (pt with relapse: 150 ng/mL) Weekend therapy: 21.7 – 25.3 ng/mL	-	None reported

(Haw, Shin, and Haw 2010) (n=13)	Abnormal renal function or liver function, hyperkalemia or hyperuricemia, hypertension (systolic > 140 mmHg and/or diastolic > 90 mmHg)	FBC, LFT, BUN, lipid studies, UA, serum Cr, IgE	At screening, every 2 mo. 24 h urine Cr and CrCl every 6 mo	1 pt with Cr ↑ > 30%. **(nagevraagd bij auteur of dit een kind was).**		Mild/moderate

BP: blood pressure, BSL: blood sugar level; BUN: blood urea nitrogen, ESR: erythrocyte sedimentation rate; FBC: full blood count, UEC: electrolytes, urea and creatinine, LFT: liver function test, Cr: creatinine; UA; urinalysis; ULN: upper limit of normal; TB: tuberculosis.
- : not mentioned/reported in study

Discussion:

Laboratory values to monitor

The values that are often monitored include FBC, creatinine, LFT, electrolytes, urea, lipids and blood pressure. Some studies also monitor blood sugar level, blood urea nitrogen, erythrocyte sedimentation rate, urinanalysis (sediment) and bilirubin. IgE and CD4:CD8 ratio are sometimes used to monitor the inflammation. In the ungoing TREAT trial the protocol indicates monitoring of FBC (platelet count, neutrophil count, urea and electrolytes, liver function test (ASAT, ALAT or alkaline phosphatase) and blood pressure. This is comparable to most studies, only lipid monitoring is up for debate. Personal communication with a pediatrician specialized in stem cell transplant learned they monitor lipids 2-3 times a week in the first weeks, once a week after discharge until week 12 followed by every 4 weeks until the treatment ends after 6 months. Interpretation is comparable to adults (see *Abnormal laboratory values: dose adjustment, treatment cessation or additional monitoring*)

The guideline Constitutional Eczema (CE) 2019 recommends to monitor hemoglobin, leucocytes, thrombocytes, leucocytes differentiation, ALAT, γGT, bilirubin, serum creatinine, cholesterol and triglycerides. Potassium, uric acid and urine sediment are also recommended at intake and upon request. In the Dutch guideline JIA monitoring for MTX in pediatrics is described. (NVK 2018) This could be the basis van monitoring recommendations in CsA, since the TREAT protocol for CsA is also based on MTX with additional monitoring for blood pressure.

CsA trough levels are not monitored in indications other than transplantation. (NVZA 2015) Some studies included trough levels. (Garrido Colmenero, Blasco Morente, and Tercedor Sanchez 2015, Yee and Orchard 2018) A systematic review concluded that monitoring of CsA levels is only useful in patients with additional risk factors such as impaired renal of hepatic function, interacting co-mediations or to check adherence. (Blake and Murrell 2019)

QUESTION: should lipids be a part of the standard monitoring protocol in AD? And if so, what should be the frequency?
PROPOSAL: laboratory values should be based on the TREAT protocol (uses standard protocol for paediatric dermatology in St John's hospital in UK), the majority of studies in pediatric atopic dermatitis and monitoring recommendations for MTX in JIA in the Netherlands (plus blood pressure).
MEETING 10-9-2020: monitor blood pressure, creatinine, ALAT and complete blood count.

Standard frequency of monitoring

The frequency of monitoring is not always described and dependent on study duration. The study of Yee et al focused on the monitoring of CsA in paediatric dermatology in Australia. They conclude less frequent monitoring did not result in any significant adverse events over a 15-year period. They monitored before initiation of therapy, after 1 month of therapy followed by monitoring every 3 months. All laboratory values were determined at these time points, while the Dutch guideline states cholesterol and triglycerides can be monitored 4 weeks after initiation of treatment and during maintenance therapy once a year.

QUESTION: Yee et al and the TREAT protocol perform monitoring after 4 weeks. The Dutch guideline states 12 weeks for the complete set of laboratory values. In the Dutch JIA guideline for MTX there is also full monitoring after 4 weeks. A suggestion in between would be at week 6, at week 12 and then every 12 weeks. Do we follow the recommendations abroad/for JIA or the Dutch guideline CE (not specifically for pediatrics)?
PROPOSAL: monitoring before initiation, after 4, 6 (or/and 12) weeks and 3 monthly thereafter.
MEETING 10-9-2020: no monitoring after 4 weeks, but after 12 weeks. At stable dose (in case of non-discrepant previous findings), monitor every 12 weeks.

Abnormal laboratory values: dose adjustment, treatment cessation or additional monitoring

Dose reductions (20 (TREAT)-25% (Harper) or 1 mg/kg/day (Sidbury et al. 2014)) are proposed if:
- Cr > 25 (Sidbury) - 30% (Harper) increased (in TREAT: 20% fall of eGFR)
- Blood pressure > 95% for age and sex on two consecutive measurements
- 2-3 times the ULN for liver function parameters

TREAT also mentions platelet count < $100x10^9$/L, neutrophil count <$1.5x10^9$/L (TREAT) as reason to lower the CsA dose by 20%. The measurement should be repeated weekly. Further reductions in these counts lead to more dose reduction or treatment determination.

In adults a lipid a normal profile consists of total cholesterol (< 5.5 mmol/L), LDL cholesterol (<2.5 mmol/L), HDL cholesterol (≥ 1.55 mmol/L), triglycerides < 2 mmol/L and total cholesterol/HDL cholesterol < 5. (NVKC, lipidenprofiel). In stem cell transplantation an abnormal lipid profile is usually corrected with alterations in TPV. In 1 study 2 patients developed hypertriglyceridemia, which led to treatment cessation. The authors mention the level of hyptertri-glyceridemia was not life-threatening, but they rather switched therapy than to introduce lipid-lowering therapy in children. (Yee and Orchard 2018)

In the Dutch guideline EC a 25-50% dose reduction is recommended if Cr has 2 consecutive increases of > 130%. In hypertension the addition of amlodipine 5 mg is also an option. They mention a lower limit for leucocytes of $3.0x10^9$/L and $100x10^{12}$/L for platelets. The platelet cut-off is strange, since the normal range for platelets is 150-$400x10^9$. The JIA guideline for MTX only provides recommendations for abnormal liver function tests.

In stem cell transplantation an alternative immunosuppressant is considered when eGFR decreases and CsA concentration is within normal range. If CsA is within toxic range, one CsA intake is skipped and the dose is lowered. There is no strictly defined cut-off when an intervention is needed. Usually invention is needed when GFR (Schwartz) falls below 60 ml/min/1.73m^2 or GFR decreases > 30%. (Personal communication R Bredius). This is confirmed by children nephrologists (Personal communication E Dorresteijn and M Schreuder). In the American AD guideline they specify the dose increase of 1 mg/kg/day should

be used for 2-4 weeks followed by a recheck of the renal function. If renal function improves (but is not back to normal): hold lower dose, otherwise stop CsA. (Sidbury et al. 2014)

QUESTION: what should be recommendations for high BP, platelet count, neutrophil count (or leucocyte count?) and lipids (if added to standard protocol)?
PROPOSAL: provide a dose reduction for Cr increase with more than 30%. The recommendation for LFT should be based on the JIA guideline.
MEETING 10-9-2020: no recommendations for high BP or creatinine.

Other recommendations to monitor (comorbidities, vaccinations, contraception)
For CsA adequate contraception and recommendations regarding life vaccines are applicable. (Irvine et al. 2018) Hypertension is one of the exclusion criteria in TREAT, but also in other studies. For retrospective studies it is not always mentioned, but it is likely that the prescribers selected patients without hypertension for CsA treatment. One case shows successful treatment with CsA in a child with hypertension, since they speculated the hypertension was due to the uncontrolled atopic dermatitis. (Ahmed, Milford, and Moss 2002) CsA even lowered the blood pressure. None of the patients in the studies developed hypertension.

In the Dutch guideline CE HIV, HBV/HCV should be tested before initiation to rule out active infections. In the TREAT protocol for MTX it is mentioned that dermatologists in > 30 countries agreed HIV and hepatitis B/C testing is not required for children receiving MTX (Gerbens et al. 2019). This screening should only be performed when there is a history of risk factors. These risk factors are very rare in children.

PROPOSAL: cave hypertension remains, it is not an absolute contra-indication. Screening for HIV and hepatitis B/C is not recommended. Patients should be informed about live vaccines and sufficient contraception. CsA can have effects on the fetus, but can be used during pregnancy if necessary. (Teratology Information Centre)
MEETING 10-9-2020: approved.

5. Side effects

Bone mass
Two studies investigated an effect of CsA on bone mineral density (BMD). In one study an association was found between CsA use and lubar spine bone mineral apparent density (also after correction for the corticosteroid index). (Pedreira et al. 2007) In the other study there was a trend to a lower BMD, but this was not significant. Since corticosteroids were also used, it is difficult to make sure the effect was due to CsA. (van Velsen et al. 2010)
PROPOSAL: do not add to side effects: limited evidence and no studies after 2010.
MEETING 10-9-2020: approved.

Pseudotumor cerebri
There are 5 case reports describing pseudotumor cerebri (PC) in patients using CsA. In 1 7-year old using 3.5 mg/kg/day developed PC 2.5 months after initiation of CsA. Treatment determination resolved the PC, although the retinography needed treatment with diazepam and acetazolamide. (Blasco Morente et al. 2015) In the other 4 case reports CsA was used for a different indication. (Somech and Doyle 2007, Costa et al. 2010, Büscher et al. 2004, Bilginer et al. 2010, Dogulu et al. 2004).
PROPOSAL: add pseudotumor cerebri to 'bijwerkingen bij kinderen'
MEETING 10-9-2020: approved.

Handbook 1 BNF for children 2018-2019	Short-term treatment of severe atopic dermatitis where conventional therapy ineffective or inappropriate (administered on expert advice) (**by mouth**): Child: Initially 1.25 mg/kg twice daily (max. per dose 2.5 mg/kg twice daily) usual maximum duration of 8 weeks but may be used for longer under specialist supervision, if good initial response not achieved within 2 weeks, increase dose rapidly up to maximum Short-term treatment of very severe atopic dermatitis where conventional therapy ineffective or inappropriate (administered on expert advice) (**by mouth**): Child: 2.5 mg/kg twice daily usual maximum duration of 8 weeks but may be used for longer under specialist supervision	Remarks: Cautions: - in atopic dermatitis, active herpes simplex infections – allow infection to clear before starting (if they occur during treatment withdraw if severe) - in atopic dermatitis, *Staphylococcus aureus* skin infections – not absolute contra-indication providing controlled (but avoid erythromycin unless other alternative)
Handbook 2 Pediatric & neonatal dosage handbook 25th edition	Indication not mentioned	
Handbook 3 IBM Micromedex®	Atopic dermatitis (**oral**): In an uncontrolled trial, oral cycloSPORINE was found to be effective for the treatment of severe atopic dermatitis in 27 children. The patients received a dose of 5 mg/kg/day in 2 divided doses for 6 weeks (Berth-Jones 1996)	
Handbook 4 Drug prescribing in renal failure, 5th edition 2007	GFR 30-50: 100% GFR 10-29: 100% GFR <10: 100% IHD: 100% PD: 100% CRRT: 100%, monitor serum concentrations (B)	Standard dosage: Consult institutional transplant protocol or other pediatric reference

General discussion:
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Additional information:
Renal function:
- *Current KF*: Niet geven aan patiënten met een nierfunctiestoornis.
  Bij patiënten met het nefrotisch syndroom en met een verstoorde nierfunctie, mag de initiële dosis 2,5 mg/kg/dag niet overschrijden.
- *KNMP*: Bij verminderde nierfunctie is bij aanvang van de behandeling aanpassing van de dosering niet noodzakelijk. Het risico op nefrotoxiciteit verschilt niet tussen patiënten met verminderde nierfunctie en patiënten met normale nierfunctie.
  Bij nefrotisch syndroom adviseert de fabrikant wel een lagere aanvangsdosis in geval van verminderde nierfunctie bij volwassenen van aanvankelijk 2.5 mg/kg lich.gewicht per dag in 2 doses. Bovendien adviseert de fabrikant de dosering met 25-50% te verlagen als de serumcreatinineconcentratie meer dan 30% boven de uitgangswaarde stijgt en bij meer dan 1 bepaling op dit niveau blijft.
  Bij uveïtis, psoriasis, constitutioneel eczeem en reumatoïde artritis adviseert de fabrikant de dosering met 25-50% te verlagen als de serumcreatinineconcentratie meer dan 30% boven de uitgangswaarde stijgt en bij meer dan 1 bepaling op dit niveau blijft. Ciclosporine moet worden gestaakt als dosisverlaging niet binnen 1 maand tot het gewenste effect leidt.
- *SmPC*: Ciclosporine ondergaat een minimale eliminatie via de nieren en de farmacokinetiek ervan wordt niet in sterke mate beïnvloed door een nierfunctiestoornis. Vanwege het nefrotoxisch potentieel is een nauwkeurige controle van de nierfunctie echter aanbevolen. (zie KNMP advies).
- *Pubmed*: see monitoring table
- *Proposa*l: incorporated in monitoring proposal. If there is renal dysfunction before initiation, selection of another, non-nephrotoxic immunosuppressant would be preferred. If the benefits of CsA outweigh the risks, the lowest possible dose could be initiated and titrated to the lower limit of the therapeutic range. (Personal communication E Dorrestein and M Schreuder).

Pharmacogenetics KNMP: none

Obesity: Calculate dose with ideal body weight (IBW). Close monitoring is recommended due to the narrow therapeutic window. Obese children require lower maintenance doses for equivalent serum concentrations when compared to lean controls. (Ross et al. 2015)
PROPOSAL: add information to AD, dose, potentially also for other indications (comparable to current AZA recommendation in NKFK).
MEETING 10-9-2020: approved.

Proposal meeting (10/09/2020):

Section	Proposal	Results meeting
Dosering	Change lower age limit from 2 y to 1 y	Approved
Dosering	Change initial dose from 5 mg/kg/day in 2 doses to 3-5 mg/kg/day in 2 doses. Remove 'gedurende 3-6 weken'	Partly approved, do not remove 'gedurende 3-6 weken'
Dosering	Change maintenance dose from 2.5-3 mg/kg/day in 2 doses to 2-5 mg/kg/day in 2 doses. Add information about weekend therapy and gradual decrease	Approved, but rephrase weekend therapy and add reference
Dosering	Add information about treatment duration (3 mo - > 1 y) and evaluation time (4 wks)	Approved, but rephrased
Dosering	Remove current text: Uitsluitend bij patiënten die onvoldoende respons vertonen op intensieve lokale therapie. Toepassing uitsluitend door dermatoloog met ervaring met dit middel voor deze indicatie. Intensieve controle van bloeddruk en laboratoriumwaarden noodzakelijk. Replace by (identical to psoriasis):	Replace by general sentence: 'Behandeling door of na overleg met een kinderarts-specialist (dermatoloog) die ervaring heeft met gebruik van ciclosporine voor deze indicatie'

	Toepassing uitsluitend door dermatoloog met ervaring met dit middel.	
Dosering	Add information about children with obesity (lower dose and strict monitoring).	Add to warnings and precautions
Waarschuwingen en voorzorgen bij kinderen	Add monitoring information:	
Waarschuwingen en voorzorgen bij kinderen	Bij start controle van bloeddruk, creatinine, leverenzymen (ALAT voldoende) en volledig bloedbeeld.	Approved, but onlyl ALAT, without liver enzymes
Waarschuwingen en voorzorgen bij kinderen	6 weken na start, 12 weken na start en na elke dosisverhoging opnieuw controle.	Approved
Waarschuwingen en voorzorgen bij kinderen	Vervolgens bij stabiele dosis elke 12 weken controle (bij niet afwijkende eerdere bevindingen).	Approved
Waarschuwingen en voorzorgen bij kinderen	Bij afwijkende labwaarden gelden de volgende aanbevelingen: o Bloeddruk bij 2 metingen …..% verhoogd: verlaag dosis en monitor elke …. weken o Creatinine bij 2 metingen > 30% verhoogd: bepaald CsA concentratie. Indien toxisch: verlaag dosis en monitor elke …. weken. Indien niet toxisch: overweeg een ander immunosuppressivum. o Leverenzymen > 2x normaalwaarde: verlaag dosis en monitor elke 4-6 weken. Bij > 3x normaalwaarde: staak tijdelijk en evalueer bij herstart de laagst mogelijke veilige dosering. o Bij trombocyten < 100x109/L en/of neutrofielen <1.5x109/L: verlaag dosis en overleg eventueel met hematoloog. Monitor wekelijks.	Partly approved, remove sentences about blood pressure and creatinine
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan vaccinatie adviezen tijdens CsA gebruik.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan adequate anticonceptie/kinderwens. CsA kan indien noodzakelijk gebruikt worden tijdens zwangerschap, maar extra controle van de pasgeborene is nodig.	Approved
Bijwerkingen bij kinderen	Pseudotumor cerebri is gemeld in 5 casus.	Approved
Nierfunctiestoornissen bij kinderen > 3 maanden	Change the current recommendation to: Heroverweeg de indicatie bij patiënten met een nierfunctiestoornis. Indien de indicatie opweegt tegen de (potentiele) nefrotoxiciteit: start zo mogelijk met een lage dosis (2,5mg/kg/d in 2 doses) en titreer naar de ondergrens van de streef spiegel. Controleer naast de spiegel ook regelmatig de nierfunctie.	M. Schreuder will take a look at this after the meeting

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Kinderformularium: methotrexate

Date literature search: 05-2020 Saved in Pubmed? ☒

1. National registration/guidelines

AD: atopic dermatitis; AUC: area under the curve; CBC: complete blood count; CE: constitutional eczema; Cr: creatinine; CXR: chest radiograph; diff: differential; DLQI: dermatology quality of life index; EASI: Eczema area and intensity index; HIV; human immunodeficiency virus; IGA: investigator global assessment; JIA: juvenile idiopathic arthritis; MTX: methotrexate; NRS: numeric rating scale; POEM: patient oriented eczema measure; TB: tuberculosis.

Source	Evidence	Effect	Remarks
Ref. 1a Jylamvo 2 mg/ml drank 31-10-2019	SmPC	**4.2** **Atopische dermatitis wordt niet genoemd** Oncologie: *kinderen*: zie gepubliceerde behandel-protocollen. Doses zijn meestal gebaseerd op het lichaamsoppervlak van de patiënt en de onderhouds-behandeling is langdurig. Polyartritische vormen van actieve, ernstige JIA: *kinderen ≥3 jaar*: 10-15 mg/m² 1x per week. In therapieresistente gevallen dosering verhogen tot 20 mg/m²/week. Als de dosis wordt verhoogd, is wel een hogere controlefrequentie geïndiceerd. Pediatrische patiënten Het gebruik bij kinderen <3 jaar wordt niet aanbevolen wegens onvoldoende gegevens over de werkzaamheid en veiligheid voor deze patiëntengroep. Frequentie, type en ernst van bijwerkingen bij kinderen zullen naar verwachting dezelfde zijn als bij volwassenen. **5.2** Een gerandomiseerde studie bij kinderen met JIA (2,8 - 15,1 jaar) heeft uitgewezen dat er een grotere orale biologische beschikbaarheid is van MTX in nuchtere toestand. Bij kinderen met JIA steeg de dosisgenormaliseerde AUC van methotrexaat met de leeftijd van de kinderen. De AUC was lager dan bij volwassenen. De dosisgenormaliseerde AUC van de metaboliet 7-hydroxymethotrexaat was niet afhankelijk van leeftijd.	Reumatologische/dermatologische aandoeningen Poly-artritische vormen van actieve, ernstige JIA bij adolescenten en kinderen ≥3 jaar wanneer de respons op NSAID's onvoldoende is. Patiënten met JIA altijd doorverwijzen naar een reumatologieteam dat is gespecialiseerd in de behandeling van kinderen/ adolescenten. Voorstel: Add pediatric PK information
Ref. 1b Metoject oplossing voor injectie 5-9-2019	SmPC	**Aanvulling op bovenstaande in 4.2:** Vanwege de beperkte beschikbaarheid van gegevens over IV gebruik bij kinderen en adolescenten, is de parenterale toediening beperkt tot subcutane injectie.	

<table>
<tr><th colspan="3">National guidelines</th></tr>
<tr><td>Richtlijn constitutioneel eczeem
(NVDV 2019)</td><td><u>Methotrexaat (off-label)</u>

CE die niet voldoende reageert op lokale therapie:
>2 jaar: 0,2 – 0,4 mg/kg/dosis 1x per week.
Bij voorschrijven van MTX is intensieve controle van laboratoriumwaarden noodzakelijk. Klinisch effect treedt pas op na 8-12 weken. Tijdens het gebruik van MTX dienen regelmatig controles plaats te vinden in verband met bijwerkingen, o.a. in de vorm van been-mergsuppressie en hepatotoxiciteit.
De therapietrouw wordt aanzienlijk verhoogd bij een éénwekelijkse orale dosis. Bij gastro-intestinale klachten kan inname volgens het Weinsteinschema of toediening via éénwekelijkse injecties mogelijk verlichting geven. Om vergissing in dosering te voorkomen wordt geadviseerd alleen tabletten van 2,5mg MTX voor te schrijven.

Monitoring:
-Huidinspectie (IGA en controle cutane maligniteit) en jeuk (NRS). Aanvullend kunnen EASI, POEM en DLQI gebruikt worden.
- Bloedcontroles:

Tabel 16. Monitoringsschema behandeling met MTX bij CE
<table><tr><th rowspan="2">Parameter</th><th rowspan="2">Bij intake</th><th colspan="3">Periode in weken</th><th rowspan="2">Tijdens onderhouds-dosering (elke 3-6 mnd)</th></tr><tr><th>< 4</th><th>8</th><th>12</th></tr><tr><td>IGA en NRS*</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr><tr><td>Bloedonderzoek</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Hb, leukocyten, trombocyten</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr><tr><td>leukocyten differentiatie</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr><tr><td>ALAT, γ-GT</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr><tr><td>serum creatinine</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr><tr><td>Urinesediment**</td><td>x</td><td></td><td></td><td></td><td></td></tr><tr><td>HIV§</td><td>x</td><td></td><td></td><td></td><td></td></tr><tr><td>HBV/HCV§</td><td>x</td><td></td><td></td><td></td><td></td></tr><tr><td>Zwangerschap§</td><td>x</td><td></td><td></td><td></td><td></td></tr><tr><td>X-Thorax***</td><td>x</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="6">Grenswaarden: Leukocyten <3,0 x 10^9/L; Trombocyten <100 x 10^12/L; ALAT en/of γ-GT >2x de bovengrens van normaalwaarde → overleg/verwijzen MDL arts; Bij stijging van serum creatinine > 130% boven de uitgangswaarde van de patiënt, dient de frequentie van controles geïntensiveerd te worden en evt. de dosering aangepast te worden.</td></tr></table>* Aanvullend kunnen de EASI, POEM of DLQI gebruikt worden.
** Standaard bij intake. Verdere monitoring op indicatie.
*** De werkgroep adviseert na overleg met de NVALT dat er een baseline X-thorax van maximaal 6 maanden oud beschikbaar moet zijn ter vergelijking bij verdenking op MTX-pneumonitis.
§Uitsluiten (anamnestisch of testen)
Op indicatie: serum albumine (bijv. bij verdenking op hypoalbuminemie of bij patiënten die andere medicatie gebruiken met sterke binding aan serumalbumine), urinezuur
NB: de richtlijn geeft geen informatie over de afhandeling van verhoogde labwaarden.</td><td><u>Dosering (kinderen)</u>
De genoemde dosering is conform de dosering bij psoriasis volgens het kinderformularium, er is geen dosering specifiek voor de behandeling van CE bekend. Als suppletie wordt foliumzuur in een dosering van 5-10 mg 24 uur na MTX inname geadviseerd. [NKFK 2019].

MTX dient voorgeschreven te worden door een specialist in kinderdermatologie. De dosis dient individueel vastgesteld te worden en de laagst mogelijke dosis dient toegepast te worden. Voor start van de behandeling dient overlegd te worden met een kinderarts met ruime ervaring met het voorschrijven van MTX (kinderreumatoloog).

Het advies is gebaseerd op El-Khalawany en Deo.</td></tr>
<tr><th colspan="3">International guidelines</th></tr>
<tr><td>Guideline</td><td>Guidelines of care for the management of atopic dermatitis. Section 3.
(Sidbury et al. 2014)

<u>Summary (El-Khalawany 2013)</u>
At the time of literature review, there were no prospective data on MTX use in children for the treatment of atopic dermatitis. Since then, one 12-week study showed a slower onset of effect compared to low-dose cyclosporine, but increased time before relapse on discontinuation. Multiple studies regarding its use in pediatric psoriasis patients show MTX to be a safe, effective, and well tolerated medication.
The side effect profile for children on MTX commonly includes GI complaints such as stomatitis, nausea, and vomiting, but the same potential risks exist in children</td><td>Indication: refractory AD
Dosage: 0.2-0.7 mg/kg/week. Consider test dose 1.25-5 mg. Check CBC in 5-6 days; if normal, increase dose gradually to desired therapeutic effect.</td></tr>
</table>

	as they do in adults. Most adverse effects of MTX are reversible upon dose reduction, route modification, or altered dosing schedule. As with adult patients, the lowest effective dose to achieve the desired results should be given. Monitoring (in general): At baseline: CBC/diff/ platelets, renal function, liver function, Hepatitis B and C, TB testing, HIV if indicated, HCG if indicated, pulmonary function tests if indicated. Follow-up: CBC/diff/platelets, renal function every 6-12 mo, liver function weekly for 2-4 wks and 1 wk after each major dose increase, then every 2 wks for 1 mo and every 2-3 mo while on stable doses. HCG if indicated, annual TB testing. Liver enzymes transiently rise after MTX dosing; obtain labs 5-7 days after the last dose. Significant elevations of liver enzymes: - exceeding 2× normal, check more frequently - exceeding 3× normal, reduce the dose and recheck - exceeding 5× normal, discontinue Avoid in patients at risk for hepatotoxicity Liver biopsy may be considered at 3.5- 4.0 g of cumulative methotrexate in adults No standard liver biopsy recommendations for children Consider pulmonary function tests prior to initiation and during therapy in consultation with a pulmonologist for patients with asthma or chronic cough, or consider alternative therapies CXR if respiratory symptoms arise	
Guideline	**Guidelines of care for the management of atopic dermatitis. Part II.** (Wollenberg et al. 2018) <u>Summary</u> (El Khalawany 2013) • MTX may be used (off label) for treatment of AE in both adults and children. • The recommended dosing regimen is similar or slightly lower compared to psoriasis. • As MTX is teratogenic, men and women of childbearing potential must use effective contraception during therapy.	Starting dose children: 10-15 mg/m^2/week Maintenance dose children: Increase 2.5-5 mg/week, decrease 2.5 mg/week to effective/lowest effective dose.

2. Kinetics

- Plasma protein binding: ~50% reversible (IM)
- Metabolism: hepatic and intracellular polyglutamisation to active polyglumate metabolites.
- Excretion: ~80-90% is renally excreted (as MTX) and <10% is excreted by feces. With increasing oral doses, the percentage of excretion in the feces increases.
- TDM (NVZA): In general there is no TDM for indications other than oncology. 24 h after infusion the concentration should be below 10 µmol/L to avoid toxicity. The Cmax after a dose of >1000 mg/m^2 is ~ 500-1500 µM.

3. Atopic dermatitis

Articles regarding use of MTX in severe, refractory atopic dermatitis in paediatric patients are summarized in the table below. Some studies also included patients with nummular eczema. Since this condition is comparable to AD, these studies are included. All studies are observational unless stated otherwise.

Study	Age (start MTX)	Dose (week)	Folic acid	Oral/ SC	Outcome	Time to initial response	Duration
(Roberts and Orchard 2010), N=25 Case-series Indication: nummular eczema	Mean 7 y (3-16 y)	Initial dose: 10 mg in 24 pt and 5 mg in a 3 y old (increased to 10 mg after 4 wks). Treatment dose 5-15 mg/week.	5 mg 3-4 days after MTX	Not described	16/25 pt cleared their eczema. There were followed for 9 mo (mean) after MTX treatment was terminated. 3 pts relapsed and were treated with MTX again. They remained clear (median follow up 14 mo). 3 pt still using MTX were almost clear (mean treatment duration 12 mo). 3 pt responded, but not enough to terminate MTX treatment. 2 pt with very severe eczema received adjuvant UVB treatment and continued MTX at a lower dose (mean treatment duration 23 mo)	Not described	Mean 10.5 mo (3-30 mo) (n=16)
(Park, Yeom, and Kim 2013) N=1, case	5 y	7.5 mg, divided in 3 doses with 12 h interval Reduced to 7.5 mg biweekly after 7 wks	1 mg daily	Oral	SCORAD reduced by >50% (from 61 to 28) after 7 wks. In the next 3 months there was no relapse and clinical improvement continued. There were no side effects or laboratory abnormalities	7 wks	17 wks
(El-Khalawany et al. 2013) N=20 Unblinded RCT	Mean 11.6 y ± 1.52 y	Test dose 5 mg, 7.5 mg, divided in 3 doses with 12 h interval.	0.4 mg day af-ter last dose MTX	All oral	Mean absolute reduction in SCORAD: 9.95 (4 wks) → 19.75 (8 wks) → 26.25 (12 wks) → 24.90 (24 wks). Pts relapsed at week 20 (mean). Time to initial response and time te relapse were late compared to CsA.	3-5 wks	12 wks, follow-up 24 wks
(Deo et al. 2014) N=31 retrospective	Mean 10 y (3-18 y)	Median initial dose (treatment dose): 0-5 y: 5 mg (7.5 mg) 6-10 y: 10 mg (10 mg) ≥ 11 y: 15 mg (15 mg)	5 mg 2 times a week (not on MTX day)	Oral at initiation, 1 3 y old switched to sc	75% of pts showed improvement. Total treatment duration was higher in improved group (mean 14 mo vs mean 6 mo). 3 pt stopped treatment temporarily: administration problems in 1 pt, relapse 1 mo after MTX cessation in 1 pt and infected eczema in 1 pt.	8-12 wks	Median 9.5 mo (2-38 mo)
(Rahman et al. 2014) N=46 (30 with AD) retrospective	Median 8 y (2-17 y	Mean initial dose 0.48 mg/kg (pt < 30 kg) and 0.33 mg/kg (>30 kg). Max 15 mg. Treatment dose not described.	Not described	Initial oral, some switch to sc	38/46 pt were responders 11 pt were late responders (> 12 wks and after dose modification or switch to sc administration) No adverse events leading to dose decrease or treatment termination.	27/38 pts: 12 wks	Mean 363 d
(Dvorakova, O'Regan, and Irvine 2017) N=47 retrospective	Mean 11.6 y (2-18 y)	Test dose 5 mg, 0.3-0.5 mg/kg. Dose increase when response is insufficient Mean treatment dose: 0.34 mg/kg.	Not described	40 pt oral, 1 pt sc, 6 pt oral + sc	44/47 pts treated with MTX completed first 3 mo. Mean baseline IGA 4.25 → 3-5 mo treatment: 2.8 → 10-14 mo 1.9. This indicated further continued improvement with long-term MTX treatment. At data collection, 30 pt were still using MTX (first course) and 3 pt (out of 14 pt who completed the first course of MTX) used a second course of MTX after relapse.	11.3 wk (range 3-24 wks)	Mean 17.2 mo (5-33) in 14 pt

					31 pt had a flare-up during MTX treatment, treatment: topical CS, MTX dose adjustment or both.		
(Yee and Orchard 2018) N=97 retrospective	Mean 9.0 y (2-18 y)	0.4-0.6 mg/kg/week. Start with 50% of dose for 2 wks and monitor clinical side effects	Not described	Probably oral	-	-	Mean 758 d (2 d – 148 mo)
(Knöpfel et al. 2018) N=28 Retrospective N=10 AD + nummular eczema	Mean 7.8 y (6.1-9.4)	Mean starting dose: 0.29 mg/kg/week in 2 doses with 12 h interval. Dose increase in 15 pt (0.12 mg/kg/week) due to insufficient response. Mean duration initial dose in these pts: 4.6 mo (1.3-8.1 mo)	5 mg 12 h after last dose MTX	Oral at initiation: 3 pts switched to sc.	Final visit (mean 13.4 mo): 10 pt complete clearance, 13 marked improvement, 4 pt mild improvement and 1 pt with treatment failure (dose increase to 0.42 mg/kg/week was tried without success). 14 pts stopped using MTX during follow-up (10 complete clearance, 3 marked improvement and 1 treatment failure). 14 pts still using MTX (10 marked improvement, 4 mild improvement) had a median treatment duration of 9.4 mo (5.9-39 mo). In 11.5 mo (mean) after MTX treatment 3/10 pt with complete clearance relapsed. MTX was successfully restarted.	At 4 wks: most pt had mild response (19 pt). At 3 mo: all pt improved (mild/ marked), 1 complete clearance	Median 12.6 mo (9.2-16 mo). 14 pts were still using MTX
(Purvis et al. 2019) N=43 retrospective	Median 10 y (IQR 7-12)	10 mg/m^2, rounded to the nearest 2.5 mg, max 15 mg. Up- and down titration was applied Median dose: 0.33 mg/kg (IQR 0.26-0.4)	5 mg once weekly	All oral	Before MTX, 14 pts required hospitalization for AD. During MTX, 6 pts were hospitalized. (p=0.07) Parents judgement of AD at the end of MTX treatment in 30 pts (median treatment duration 18 mo): 23/30 pt: a lot better; 2/30 pt: slightly better; 5/30 pts: no change. 10/25 pts relapsed after 20 mo (median): AD severity was het same as before MTX in 6 pt. In 4 pt the relapse was mild.	Not described	Median 17 mo (IQR 7.5-20 mo)
(Anderson et al. 2019) N=55 retrospective	Mean 10.6 y (3-19.5 y)	Mean initial dose: 0.37 mg/kg (0.12-0.73) Mean highest dose oral: 0.45 mg/kg (0.12-1.00) Mean highest dose sc: 0.50 mg/kg (0.22-0.77) Mean duration initial dose: 4.5 mo (1.0-24.5)	Not described	38 pt oral, 2 pt sc, 15 pt oral + sc	42/55 pt showed improvement (not defined in IGA points) Mean baseline IGA 4.2 → 6-9 mo treatment: 2.9 → 12-15 mo 2.4. Final visit before discontinuation: IGA 2.7. After MTX, 8 pt switched to AZA, CsA or MMF, 27 pt used topical therapy and 12 pt used 'other therapy' Total treatment duration was higher in improved group (mean 17.4 mo vs mean 8.4 mo). The oral dose was highest in the unimproved group (mean 0.56 mg/kg vs mean 0.41 mg/kg).	39/42 responders < 2 mo, 2 3-4 mo and 1 5-6 mo	Mean 15.3 mo (3.0-39.0)
(Taieb et al. 2019) N=26 retrospective	Median 12 y (7-14 y)	0.25 mg-0.6 mg/ (kg.week). Divided in 2-3 doses with 12 h interval. If no response at 8 wk: increase by 2.5 mg/week.	5 mg 24 h after last MTX dose	All oral	After 6 mo14/26 pt had clinical improvement (IGA decrease > 2 points) compared to baseline and 3 mo. Previous use of systemic CS was associated with a higher response rate. 14 pt were still successfully treated with MTX at the end of follow-up (median 25 mo). 10 pt stopped MTX due to clinical improvement and used first-line AD medications (topical products and antihistamines). 2 poor responders stopped MTX and started CsA	All 14 responders had clinical improvement after 3 mo.	Median 14 mo (IQR 7-26.5 mo)

AD: atopic dermatitis; AZA: azathioprine; CS: corticosteroids; CsA: ciclosporin; IGA: investigator global assessment; MMF: mycophenolate mofetil; MTX: methotrexate; sc: subcutaneous; SCORAD: SCORing Atopic Dermatitis.

Discussion:

Age limits

In most studies the range of ages has a lower limit of 3 years or above. Some studies mention 2 year olds as the youngest included patients (Yee and Orchard 2018, Dvorakova, O'Regan, and Irvine 2017, Rahman et al. 2014). The Dutch guideline Constitutional eczema and the current NKFK dosing recommendation for psoriasis also mention 2 year as the lower limit.

PROPOSAL: the age limits for atopic dermatitis are 2-18 year old.
MEETING 10-09-2020: approved.

Treatment duration

Treatment duration has a great variation and depends on the study duration. If a range of treatment duration was provided, it was not always clear if shorter treatment durations were patients with insufficient response. Two studies provide treatment duration per group of responders: mean 14 months and 17.4 months in responders vs. 6 months and 8.4 months in non-responders. (Deo et al. 2014, Anderson et al. 2019) The (unblinded) RCT only investigated 12 wks of treatment. (El-Khalawany et al. 2013) In retrospective studies treatment duration is usually much longer (up to 148 months (Yee and Orchard 2018)).
In the trial protocol for the RCT TREAT (comparing MTX and CsA for atopic dermatitis in children) MTX is used for 36 weeks with a follow up period of 24 weeks after cessation. (Irvine et al. 2018)

Current NKFK recommendations and the Dutch guideline Constitutional eczema do not recommend a treatment duration as well. (NVDV 2019) The JIA guideline does mention it should be considered to decrease MTX dose after 9 months of remission, followed by termination of treatment. (NVK 2018)

QUESTION: can we copy the recommendation in the JIA guideline regarding treatment termination for AD?
MEETING 10-09-2020: yes.
PROPOSAL: an optimal or maximum treatment duration cannot be provided. Mention the termination after 9 months of remission in the 'precautions' section.
MEETING 10-09-2020: add the following about treatment duration: 'If there is no improvement within 3 months with the highest dose tolerated, methotrexate discontinuation should be considered.'

Initial dose

Most studies have a low initial dose and increase the dose based on clinical response. In 1 case of a 5 year old boy there was an opposite titration schedule: the initial dose was 7.5 mg (divided in 3 doses) which was reduced to 7.5 mg biweekly after 7 weeks. (Park, Yeom, and Kim 2013) In 3 studies younger children were treated with a different initial dose than older children. (Roberts and Orchard 2010, Deo et al. 2014, Rahman et al. 2014). Children aged 3-5 years were treated with 5 mg/day or with a higher initial dose per kg body weight (0.48 mg/kg in children < 30 kg vs 0.33 mg/kg in children > 30 kg). One study used an initial dose of 10 mg/m^2, rounded to the nearest 2.5 mg. (Purvis et al. 2019) For children up to 5 years this would be 5 mg or 7.5 mg MTX. Other (initial) doses vary from 0.25 mg/kg until 0.6 mg/kg (these are based on protocol). (Yee and Orchard 2018, Taieb et al. 2019) If mean initial doses are

provided these are between 0.29 mg/kg/week and 0.37 mg/kg/week. (Knöpfel et al. 2018, Anderson et al. 2019). For older children initial doses of 10 mg were used. (Roberts and Orchard 2010, Deo et al. 2014). In one study children of ≥ 11 years even started with 15 mg/week. (Deo et al. 2014).

In other indications for MTX currently in NKFK, there is no distinction between the initial dose and the maintenance dose. For psoriasis the current dose is 0.2-0.4 mg/kg/dose, once a week. Since there is no clear distinction between the initial dose and the maintenance dose in the studies and other indications do not reflect the need for a separate initial dose, there will not be an initial dose for AD as well.

Test dose
In 2 studies a test dose of 5 mg MTX was used. (Dvorakova, O'Regan, and Irvine 2017, El-Khalawany et al. 2013). In the TREAT protocol a test dose of 0.1 mg/kg MTX is used. (Irvine et al. 2018). The purpose of this test dose is to capture rare idiosyncratic reactions caused by MTX. SmPC's advise a test dose, but the Dutch guidelines Psoriasis only recommends this in populations at high risk for adverse events, such as elderly and patients with comorbidities.

PROPOSAL: only provide one dose: a separate initial or test dose is not indicated.
MEETING 10-09-2020: approved.

Maintenance dose
Not all studies provide a mean treatment dose: some only mention a protocol dose. (Yee and Orchard 2018, Taieb et al. 2019) In one unblinded RCT a set dose was used: 7.5 mg/week. (El-Khalawany et al. 2013). This seems low when compared to the doses used in retrospective studies. The mean doses varied between 0.33 mg/kg/week and 0.45 mg/kg/week (when used sc the dose was slightly higher: 0.5 mg/kg/week). (Anderson et al. 2019, Dvorakova, O'Regan, and Irvine 2017, Knöpfel et al. 2018, Purvis et al. 2019)

In the protocol for TREAT the used dose is 0.4 mg/kg/week (max. 25 mg/week). After 12 weeks, dose adjustments are permitted (still max.25 mg/week. All doses are rounded to the nearest 2.5 mg, since 2.5 mg MTX tablets are used. (Irvine et al. 2018) In the Netherlands 2.5 and 10 mg tablets of MTX are available. Lower doses than 0.4 mg/kg/week have been used with success, so a dose range would be possible. Doses as low as 0.12 mg/kg are described. (Anderson et al. 2019). Since the specific results for patients with these low doses are not provided, 0.2-0.4 mg/kg/week seems a more valid dosing range. The low dose used in the RCT is also described by other studies as 'subtherapeutic'. (El-Khalawany et al. 2013) 7.5 mg/week would correspond with 0.13-0.19 mg/kg/week in children with a body weight between 40-60 kg. The set dose of 15 mg in children ≥ 11 years in another study is comparable to 0.25-0.357 mg/kg/week. (Deo et al. 2014). In 25 patients with nummular eczema 15 mg was also the highest dose in use. (Roberts and Orchard 2010)
Higher doses than 0.4 mg/kg/week have also been described, but it should be noted that one study mentioned the oral dose was the highest in the patients with insufficient response. (Anderson et al. 2019). The mean oral dose in responders was 0.41 mg/kg vs. 0.56 mg/kg in non-responders. The high initial dose in children < 30 kg in one study could indicate a higher dose in young children, but it is unclear what the treatment dose in these children was. There were also 16 children in this study with psoriasis or a combination of psoriasis and AD, which might indicate more complex patients. (Rahman et al. 2014)
In some studies the Weinstein schedule is applied for MTX dosing: one third of the dose every 12 h. In the Dutch guidelines for CE and psoriasis this schedule is not preferred. This schedule should only be considered if there are (gastro-intestinal) side effects. (NVDV 2019, 2017)

Oral vs subcutaneous

Subcutaneous use of MTX is usually applied if there are adverse events, administration problems (mainly in young children) or insufficient response. In one study the mean subcutaneous dose was slightly higher, but this can also be caused by the fact that patients with sc MTX were 'difficult' patients with insufficient response. (Anderson et al. 2019) The sc dose is in general the same as the oral dose (KNMP 2020), although the CE guideline mentions the sc dose can be lower due to differences in oral absorption.

QUESTION: should we include a recommendation in the oral dosing section when to switch to sc?
MEETING 10-09-2020: no, this belongs to the guideline
QUESTION: is a dose in mg/kg preferred (comparable to psoriasis) or a set dose per weight limit (comparable to Crohn's disease)? Since it will have to be rounded to 2.5 mg doses anyway, a set dose per weight limit is practical. If 0.4 mg/kg is converted to weight limits, it would be like this:

10-20 kg = 4-8 mg/week (not in Crohn's disease, proposal would be 5 mg/week).
20-30 kg = 8- 12 mg/week (in Crohn: 10 mg/week)
30-40 kg = 12-16 mg/week (in Crohn: 15 mg/week)
40-50 kg = 16-20 mg/week (in Crohn: 20 mg/week)
> 50 kg = 20-25 mg/week (in Crohn: 25 mg/week)

If the NKFK network prefers to use a dosing range, the set doses could be adjusted. Personally I think a dose per kg would be clearer if we want to include a dosing range.

MEETING 10-09-2020: the dose should be converted to a mg/m2 dosage. This will be discussed in the next meeting.

QUESTION: in the case report of a 5 year old boy a biweekly dose is used after 7 weeks of initial weekly treatment. Is this something that should be mentioned to taper off dosing?
MEETING 10-9-2020: not discussed
PROPOSAL: 0.2-0.4 mg/kg once a week for atopic dermatitis. Route of administration: oral or subcutaneous.
MEETING 10-9-2020 + 7-12-2020: no decision could be made. In April 2021 this issue is again addressed to J. van den Berg and S. de Wildt. It is agreed to change the dosage to 10-15 mg/m2.

Folic acid

Most studies use 5 mg folic acid once weekly at least 24 h after MTX administration. (Roberts and Orchard 2010, Knöpfel et al. 2018, Purvis et al. 2019, Taieb et al. 2019) 2 studies, including the TREAT trial, use 1 mg daily (except the day of MTX administration). (Irvine et al. 2018, Park, Yeom, and Kim 2013) The unblinded RCT uses 0.4 mg once a week, but this seems extremely low. (El-Khalawany et al. 2013) One study mentions 5 mg twice a week, although the highest dose in this study was 15 mg/week. (Deo et al. 2014) The Dutch guidelines of psoriasis and CE recommend 5 mg once weekly if the MTX dose is ≤ 15 mg and 10 mg if the MTX dose is above 25 mg. (NVDV 2019, 2017) The JIA guidelines does not make a distinction in MTX doses: they recommend 5 mg 24-48 h after MTX, 1 mg once daily (not on MTX day) or 5 mg once a week + 1 mg on the remaining 5 days. (NVK 2018)

QUESTION: can we copy the recommendation in the JIA guideline regarding folic acid or use the recommendation as provided in the psoriasis and CE guidelines? The literature is more in favor of the JIA guideline, since 10 mg folic acid in high(er) dose MTX has not been studies in patients with AD.

PROPOSAL: Ter voorkoming van toxiciteit wordt behandeling van MTX altijd gecombineerd met foliumzuur, eenmaal per week 5 mg, een of twee dagen na de MTX-toediening. Andere mogelijke schema's zijn 1 mg per dag (niet op de dag van MTX toediening) of 5 mg 1x per week en 1 mg 1x per dag op de andere dagen (niet op de dag van MTX toediening). (based on NKFK text for JIA and Crohn's disease).
MEETING 10-9-2020: change this into: 'To prevent toxicity, treatment of MTX is always combined with folic acid, once a week, one or two days after MTX administration'.

Evaluation time
Time to initial response is described in 8 studies and varied between 3 weeks and 6 months. The timing was often depended on planned doctors visits and it is not always clear what the magnitude of the response was. The first dose increases due to insufficient response were usually after 2-4 months. (Anderson et al. 2019, Knöpfel et al. 2018, Taieb et al. 2019). In the Dutch guidelines of psoriasis and CE dose increase is recommended in adults after 8 weeks. (NVDV 2017, 2019). None mention when MTX therapy should be discontinued: first a dose increase or switch to sc administration is recommended.

QUESTION: is a dose increase after 8 weeks something that should be mentioned in the NKFK monography? If there is no initial dose provided, I would suggest to not include this information.
PROPOSAL: do not include information about the time to evaluation.
MEETING 10-09-2020: approved.

4. Atopic dermatitis - monitoring

The articles in table 1 are also checked for information about monitoring of laboratory values. If the article provides specific recommendations, this is provided in the discussion.

Study	Excl criteria related to monitoring	Monitoring	Frequency of monitoring	Participants with lab abnormalities	Treatment alterations	Side effects in general
(Anderson et al. 2019)	-	-	-	5 pts with transient elevated transaminases 2 pt with low haematocrit and hemoglobin	3 pts with dose reduction 1 pt stopped treatment	28 pts with at least one side effect. Nausea was most common (17 pt)
(Deo et al. 2014)	-	FBC, LFT, CR. Chest X-ray and hepatitis only if clinically indicated.	At screening and every 3 mo. If parameters stable: every 6 mo	4 pt with mild, transient, elevated transaminases 2 pt with normocytic anemia (in 1 pt due to AZA)	No alterations	4 pt with minor nausea
(Dvorakova, O'Regan, and Irvine 2017)	-	-	-	16 pt with elevated trans-aminases, isolated hyper-bilirubinemia (mild, transient) 11 pt with mild lymphopenia, neutropenia, normocytic anemia (transient)	No alterations	39 pt with side effects (both clinical and in laboratory values) 1 pt discontinued treatment, 2 pt temporarily discontinued.
(El-Khalawany et al. 2013)	none	FBC, UEC, LFT, ESR, BSL, IgE, hep B and C antibodies, chest X-ray and TB	At initiation, 4 wks, 8 wks, 12 wks and at the end of follow-up	5 pt with abnormal LFT 1 pt with abnormal renal function	None All adverse effects disappeared at the end of the follow-up period.	common side-effects: ane-mia 30%, fatigue 30%, abnormal liver function 25% nausea 20%, glossitis 20%
(Knöpfel et al. 2018)	-	FBC and serum chemi-stry (incl UEC, CR, LFT and bilirubin) Screening for Hep B and C, latent TB only if indicated	At screening, after 1 wk, 1 mo and every 3 mo. Also after every dose increase	5 pt with mild, transient elevated transaminases	No alterations	10 pts with side effects
(Purvis et al. 2019)	-	FBC, CR, LFT, varicella IgG. If needed, varicella vaccination was provi-ded and MTX started 4 wks post-vaccination.	At screening, after 1 wk, 2 wks, 4 wks, 8 wks, 12 wks and then every 12 wks	No significant abnormalities (non-significant not provided)	None	5 pts with side effects (4 gastrointestinal and 1 cataract)
(Roberts and Orchard 2010)	-	FBC, UEC, CR, LFT	At screening, after 1 mo and every 3 mo.	0	None	No serious adverse events. Most common: nausea. Resolved by dose reduction or splitting up the dose.
(Taieb et al. 2019)	Hepatic or hematologic diseases or neoplasms.	FBC, blood biochemical analysis, serological tests for hep B and C	At screening, twice in mo 1 and monthly thereafter.	2 pt with elevated hepatic transaminase (2x ULN) 3 pt with anemia and leukopenia	1 pt terminated treatment due to elevated hepatic transaminase, which resolved subsequently.	9 pt with side effects

(Yee and Orchard 2018)	-	FBC, UEC, LFT	At screening, after 1 mo and every 3 mo.	24 pt: elevated hepatic trans-aminase, thrombocytopenia, lymphopenia, anemia, neutropenia, lipid profile	5 pt terminated treatment (4 pt: ↑ AST(mean 66 U/L) and ALT (mean 111 U/L), 1 pt: lymphopenia) Others returned to normal without alterations	12 pt with clinical side effects. 5 pt terminated treatment (nausea, lethargy, recurrent flu-like symptoms and intolerance)

BP: blood pressure, BSL: blood sugar level; ESR: erythrocyte sedimentation rate; FBC: full blood count, UEC: electrolytes, urea and creatinine, LFT: liver function test, Cr: creatinine; UA; urinalysis; ULN: upper limit of normal; TB: tuberculosis
- : not mentioned/reported in study

Discussion:

Laboratory values to monitor
The values that are often monitored include FBC, creatinine, LFT, electrolytes and urea. Some studies also monitor blood sugar level, erythrocyte sedimentation rate, urinanalysis (sediment) and bilirubin. In the ungoing TREAT trial the protocol indicates monitoring of FBC (platelet count, neutrophil count) urea, electrolytes and liver function test (ASAT, ALAT or alkaline phosphatase).

The guideline Constitutional Eczema 2019 recommends to monitor hemoglobin, leucocytes, thrombocytes, leucocytes differentiation, ALAT, γGT, serum creatinine and urine sediment. Albumin and uric acid are also recommended upon request. In the Dutch guideline JIA monitoring for MTX in pediatrics is described. (NVK 2018) In this guideline FBC, creatinine, LFT is recommended.
PROPOSAL: laboratory values should be based on the monitoring recommendations in the JIA guideline: FBC, creatinine and LFT.
MEETING 10-09-2020: approved.

Standard frequency of monitoring
The frequency of monitoring is not always described and dependent on study duration. The study of Yee et al focused on the monitoring of MTX in pediatric dermatology in Australia. They conclude less frequent monitoring did not result in any significant adverse events over a 15-year period. They monitored before initiation of therapy, after 1 month of therapy followed by monitoring every 3 months. All laboratory values were determined at these time points, while other studies also monitored at 1 week and/or 2 weeks after initiation. (Knöpfel et al. 2018, Purvis et al. 2019, Taieb et al. 2019, Irvine et al. 2018). In one study the monitoring was decreased to once every 6 months if parameters were stable. (Deo et al. 2014)

QUESTION: The guideline Constitutional Eczema states 4 weeks, 8 weeks and 12 weeks, followed by a 3-6 monthly check for the complete set of laboratory values. In the Dutch JIA guideline, Yee et al and TREAT monitoring after 4 weeks is recommended, followed by a 3-4-monthly check (if there are no dose alterations). My suggestion would be to adapt the JIA protocol for AD. Should we also include that 3-4 monthly follow-up or keep the 3-6 monthly check (also mentioned by Deo et al)?
PROPOSAL: monitoring before initiation, after 4 weeks and 3-4 monthly thereafter.
MEETING 10-09-2020: approved.

Abnormal laboratory values: dose adjustment, treatment cessation or additional monitoring
Dose reductions of 20% are proposed in TREAT if:
- > 2 times the ULN for liver function parameters
TREAT also mentions platelet count < $100x10^9$/L, Neutrophil count <$1.5x10^9$/L (TREAT) as reason to lower the MTX dose by 20%. The measurement should be repeated weekly.

If there is a 20% fall of eGFR in 2 consecutive measurements, a nephrologist should be consulted.
In the Dutch JIA guideline a dose reduction (unspecified) is also recommended if liver function parameters are > 2 times the ULN. The guideline also provides information about other factors that might influence the liver function parameters, how to restart and monitor MTX and when MTX should be discontinued completely. The guidelines Constitutional Eczema do not provide any recommendations about dose reductions or when lab parameters are considered abnormal.
QUESTION: should we provide a concrete dose reduction (as in TREAT) or recommend lowering dose/temporary stop and additional monitoring (Dutch JIA guideline)? And should there be any recommendations for the other lab parameters?
MEETING 10-09-2020: no and no.
PROPOSAL: provide recommendations for high ALAT/ASAT as in JIA.
MEETING 10-09-2020: only for ALAT.

Other recommendations to monitor (comorbidities, vaccinations, contraception)
Most studies screened for hepatitis B and C (1 study only when indicated). In 1 study varicella IgG was tested and vaccination was provided if needed. Chest X-ray and TB are also mentioned (standard or when indicated). In the ungoing TREAT trial and the JIA guideline varicella IgG is screened if there is uncertainty about a previous chicken pox infection. (Irvine et al. 2018, NVK 2018) Measles serology is also considered if therapy starts before the first booster vaccination. In the Netherlands the first vaccination is at 14 months, so this is not relevant in the Dutch setting. In TREAT, sexually active females should use at least two forms of contraception and have a pregnancy test before initiation of MTX. The JIA guideline recommends to refer the patient to the general practitioner for adequate contraception, but does not oblige a pregnancy test before initiation. Hepatitis B and C is only screened in patients at risk. A chest X-ray is considered in children with a high risk of tuberculosis. This is comparable to most studies, although Varicella is only mentioned in 1 other study. (Purvis et al. 2019)

The guideline Constitutional Eczema 2019 recommends to test HIV, hepatitis B/C and pregnancy should be tested before initiation. X-Thorax can be skipped if a recent X-Thorax in available (max. 6 months old). In the TREAT protocol it is mentioned that dermatologists in > 30 countries agreed HIV and hepatitis B/C testing is not required for children receiving MTX (Gerbens et al. 2019). This screening should only be performed when there is a history of risk factors. These risk factors are very rare in children.
PROPOSAL: Varicella status should be checked and IgG determined if there is uncertainty. Patients should be informed about live vaccines and sufficient contraception. Screening for HIV, hepatitis B/C and X-Thorax is not recommended.
MEETING 10-09-2020: approved.

Initial: MvR Checked: MdH Meeting: 10-9-2020

Handbook 1 BNF for children 2018-2019	Indication not mentioned	
Handbook 2 Pediatric & neonatal dosage handbook 25th edition	Indication not mentioned	
Handbook 3 IBM Micromedex®	Indication not mentioned	
Handbook 4 Drug prescribing in renal failure, 5th edition 2007	GFR 30-50: 50% GFR 10-29: 50% GFR <10: 30% IHD: 30% PD: 30% CRRT: 50%, monitor serum concentrations, the Pediatric Dosage Handbook recommends decreasing dose for CrCl 61-80 by 25% and CrCl 51-60 by 33%, (A)	Standard dosage: Refer to individual protocols

Additional information:

Renal function:

- *Current KF*: Er zijn geen gegevens bekend over doseeraanpassing bij nierfunctiestoornissen.
- *KNMP*: ClCr 10-50 ml/min: de (neven)effecten van methotrexaat (bloedbeeld, ASAT, ALAT), alsmede de nierfunctie, moeten extra worden gecontroleerd.
- SmPC Methotrexaat Accord tabl 10 mg:
  Dosis als volgt aanpassen voor patiënten met juveniele artritis, en ook voor oncologische indicaties:
  ClCr >60: 100 %
  ClCr 30-59 50 %
  ClCr <30: Methotrexaat mag niet worden gebruikt
- Pubmed: see monitoring table
- Proposal: incorporated in monitoring proposal

Pharmacogenetics KNMP: none

Obesity: Calculate dose with total body weight (TBW) or follow road map. TBW and max dosing recommended for non-oncologic processes. Adjustment of chemotherapy based on excess body weight revealed worse outcomes in obese patients. (Ross et al. 2015)

Peerreview NKFK network, 10/09/2020:

Question: higher doses of folic acid also needed in children? folic acid when? After 24-48h after gift of MTX? Not sufficiently clear in dosage advice.
Answer: M. van den Berg: usually 5 mg twice a week, sometimes also on the day of MTX and the day after. Is well tolerated. Only increase if side effects occur: either 10 mg or 1 dd 1 mg. No evidence for this. In adults, do take 10 mg of folic acid from 15 mg MTX. SO; start after 24 hours 5 mg. In case of intolerance/abnormalities, increase. Action: addition monograph: to prevent toxicity, MTX treatment is always combined with folic acid, once a week, one or two days after MTX administration
Question: maximum doses in adults usually 25 mg/week. In pJIA (children): 20 mg/m2, in juvenile dermatomyositis 20-40 mg/dose.
Answer: Depends on mg/m2 or mg/kg. Proposal max 15 mg/m2, absolute max 25 mg. Ross et al. 2015: dose by total weight. Max advised for non-oncologic indications; no max mentioned. Action: max added.
Question: preference for BSA or kg?
Answer: In children <6 months, risk of overdose with BSA. DPF generally prefers kg, easier to dose. P. Middelkamp: Less risk of underdosing when dosing on BSA. M. van den Berg: Preference for BSA, does 0.2-0.4 mg/kg correspond to 10-15 mg/m2? 0.2 mg/kg corresponds to 5 mg/m2 in younger children; in older children, 0.2 mg/kg dose is standard 5 mg lower than 10 mg/m2. ONLY Wollenberg's guideline mentions 10-15 mg/m2.
Question: Most studies in children 3 years and older. A single study describes some 2-year-olds. Based on current guideline CE 2-18 years included. Dosing recommendation JIA in KF 0-18 years.

Answer: Depending on benefit risk: no data in children < 2 years with CE. That children with JIA do receive treatment from a younger age has to do with different benefit-risk.
Question: Is the KNMP recommendation applicable to children?
Answer: M. Schreuder is will look into this.
Peerreview NKFK network, 07/12/2020:
Question: Does 0.2-0.4 mg / kg correspond to 10-15 mg / m2? When converted, mg / m2 doses give a higher dose. Suggestion based on studies is to stick to mg / kg. However, immunologists are used to and prefer to dose on a mg / m2 basis. S. Natsch: oncology uses the following conversion: 30kg = 1m2: 0.2-0.4mg / kg is similar to 6-12mg / m2.
Answer: General comment: different dose units for different indications are not recommended. Immunologist strongly recommend to stick to mg/m2. Discussion on difference in dose between eczema indication and JIA? Also in ciclosporin lower doses for eczema compared to JIA. Aimed effect=good immunosuppressive response, Effect of MTX is slow (3 months), than possible suboptimal treatment for 3-6 months. Investigate if adult dose for eczema indication is also lower than RA indication? Current published dose recommendation is mg/kg. No decision being reached on dose in mg/m2.

Proposal meeting (10/09/2020):

Section	Proposal	Results meeting
Dosering - oraal	Age limits: 2-18 y	Approved
Dosering	0.2 – 0.4 mg/kg/dosis, 1x per WEEK.	This should be converted to mg/m2 dosing; as this is more complicated than thought on beforehand, for now the mg/kg dosages is maintained. In the next meeting the mg/m2 dosage should be discussed.
Dosering	Ter voorkoming van toxiciteit wordt behandeling van MTX altijd gecombineerd met foliumzuur, eenmaal per week 5 mg, een of twee dagen na de MTX-toediening.	Remove the 5 mg, and add a link to the folic acid monograph
Dosering	Behandeling door of na overleg met een kinderarts-specialist (reumatoloog) die ervaring heeft met gebruik van methotrexaat voor deze indicatie.	Reumatoloog → dermatoloog
Dosering - subcutaan	Identical to oral	Approved
Waarschuwingen en voorzorgen bij kinderen	Add monitoring information:	
Waarschuwingen en voorzorgen bij kinderen	Bij start controle van creatinine, leverenzymen (ALAT voldoende) en volledig bloedbeeld.	Approved, but remove liver enzymes
Waarschuwingen en voorzorgen bij kinderen	4 weken na start en na elke dosisverhoging opnieuw controle.	Approved
Waarschuwingen en voorzorgen bij kinderen	Vervolgens bij stabiele dosis elke 12 weken controle (bij niet afwijkende eerdere bevindingen).	Approved
Waarschuwingen en voorzorgen bij kinderen	Bij afwijkende labwaarden gelden de volgende aanbevelingen: o Leverenzymen > 2x normaalwaarde: verlaag dosis en monitor elke 4-6 weken. Bij > 3x normaalwaarde: staak tijdelijk en evalueer bij herstart de laagst mogelijke veilige dosering.	Approved
Waarschuwingen en voorzorgen bij kinderen	Vraag na of in het verleden varicella is doorgemaakt of test bij twijfel.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan vaccinatie adviezen tijdens MTX gebruik.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan adequate anticonceptie/kinderwens. MTX is gecontra-	Replace by the information given by the Farmacotherapeutisch Kompas

	indiceerd tijdens de gehele zwangerschap door het risico op aangeboren afwijkingen.	

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Kinderformularium: Mycophenolate

Date literature search: 03-2020 Saved in Pubmed? ☒

1. National registration/guidelines

AD: atopic dermatitis; AZA; azathioprine; CBC: complete blood count; CE: constitutional eczema; diff: differential; DLQI: dermatology quality of life index; EASI: Eczema area and intensity index; IGA: investigator global assessment; HCG: human chorionic gonadotropin; HIV; human immunodeficiency virus; POEM: patient oriented eczema measure; NRS: numeric rating scale; MMF: mycophenolate mofetil; MPA: mycophenolic acid (enteric coated); TB: tuberculosis.

Source	Evidence	Effect	Remarks
Cellcept capsules, 03-12-2019	SmPC	No information about atopic dermatitis	
Myclausen tablets, 04-04-2018	SmPC	No information about atopic dermatitis	
Myfenax, capsules 08-10-2018	SmPC	No information about atopic dermatitis	
Myfortic tablets, 16-09-2019	SmPC	No information about children or atopic dermatitis	
National guidelines			
Richtlijn constitutioneel eczeem (NVDV 2019)		<u>Mycophenolaatmofetyl en mycofenolzuur (off-label)</u> CE die niet voldoende reageert op lokale therapie: *>2 jaar*: beperkte ervaring. Klinisch effect treedt pas op na 8-12 weken. Tijdens het gebruik van MMF en MPA is intensieve controle van laboratoriumwaarden noodzakelijk. Er is weinig literatuur over effecten op lange termijn (>30 weken). Op basis van twee kleine studies is MMF effectief bij kinderen >2 jaar met ernstig CE. Op lange termijn (tot 24 maanden) worden geen bijwerkingen gemeld. Monitoring: -Huidinspectie (IGA en controle cutane maligniteit) en jeuk (NRS). Aanvullend kunnen EASI, POEM en DLQI gebruikt worden. - Bloedcontroles:	<u>Dosering (kinderen)</u> De aanbevolen dosering van MMF bij kinderen is te vinden via het **kinderformularium**. MMF dient voorgeschreven te worden door een specialist in kinderdermatologie. De dosis dient individueel vastgesteld te worden en de laagst mogelijke dosis dient toegepast te worden. Het advies is gebaseerd op Heller en Waxweiler.

Tabel 14. Monitoringsschema behandeling met MMF/MPA bij CE

Parameter	Bij intake	Periode in weken			Tijdens onderhouds-dosering (elke 3 mnd)
		4	8	12	
IGA en NRS jeuk*	x	x	x	x	x
Bloedonderzoek					
Hb, leukocyten, trombocyten	x	x	x	x	x
Leukocyten differentiatie	x	x	x	x	x
ALAT, γ-GT	x	x	x	x	x
Serum creatinine	x	x	x	x	x
HIV§	x				
HBV/HCV§	x				
Zwangerschap§	x				

* Aanvullend kunnen de EASI, POEM of DLQI gebruikt worden.
§ Uitsluiten (anamnestisch of testen)
Op indicatie: urinezuur

International guidelines		
Guideline	**Guidelines of care for the management of atopic dermatitis. Section 3.** (Sidbury et al. 2014) Summary (solely based on Heller et al. 2007) Mycophenolate mofetil should be considered a relatively safe alternative systemic therapy for pediatric patients with refractory AD. Patients aged 2 years and older have been treated with MMF as monotherapy for severe AD with benefit and without hepatic, hematologic, or infectious sequelae. No long-term efficacy or safety profiles exist at this time. Monitoring (in general): At baseline: CBC/diff/ platelets, renal function, liver function, TB testing, HIV if indicated, HCG if indicated. Follow-up: CBC/diff/platelets, liver function every 2 wks for 1 mo, then monthly for 3 mo, then every 2-3 mo thereafter. HCG if indicated, annual TB testing.	Indication: refractory AD Age: 2-18 y Dosage: 600 – 1200 mg/m^2 ~ young child 40-50 mg/kg/day ~ adolescents 30-40 mg/kg/day Administration: Duration: up to 24 mo Based on (Heller et al. 2007) Proposal: Basis for indication atopic eczema, add to references
Guideline	**Guidelines of care for the management of atopic dermatitis. Part II.** (Wollenberg et al. 2018) Summary (based on Heller et al. 2007 and Waxweiler et al. 2011) • MMF may be used for treatment of AE in children or adolescents. • As MMF and MPA are both teratogenic, men and women of childbearing potential must use effective contraception during therapy.	Indication: Atopic eczema (AE) Dose: 20-50 mg/kg/day, increase every 2-4 weeks up to 30-50 mg/kg/day

2. Kinetics

- Plasma protein binding: ~97% (IM)
- Metabolism: UGT1A9 to inactive phenol glucuronide (most part) and active acyl glucuronide (minor part). Phenol glucuronide is subject to enterohepatic circulation and is re-converted to mycophenolic acid. (IM)
- Excretion: Several transporters involved, such as OATP, MRP2 and BCRP. Metabolites are renally excreted (~93%) and by feces (~6%), < 1% unchanged (IM)
- TDM (NVZA): through level renal and liver transplant: 1.3 mg/L (with ciclosporin) or 1.9 mg/L (with tacrolimus); heart transplant: 2.0 mg/L (immuno assay) or 1.2-3.5 mg/L (HPLC); stem cell transplant: > 1.0 mg/L, toxic at > 15 mg/L. AUC estimates bid: 30-60 mg.h/L in the first 6 months of treatment.

3. Atopic dermatitis

AD: atopic dermatitis; AZA: azathioprine, MMF: mycofenolic mofetil; MTX: methotrexate

Evidence	Effect	Remarks
Ref. 3a Case series, n=12 (C)	**Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetyl** (Waxweiler, Agans, and Morrell 2011) Summary: 12 children initially treated with AZA switched to MMF, because of intolerance and/or treatment failure of AZA. In 8 children symptoms improved, 4 children did not improve. The mean onset of initial improvement was 3.9 weeks. 3 children treated with MMF experienced a cutaneous infection. The most common side effect were gastro-intestinal complaints (n=3). In one 14 y old boy dose adjustment was needed due to a low haemoglobin level. There was no wash-out between AZA and MMF treatment, so a late effect of AZA cannot be ruled out.	Indication: atopic dermatitis Age: 11-15 y + one 4 year old Dosage: 20-40 mg/kg/day Administration: - (presumably oral) Duration: 0.5-20 months Proposal: Basis for indication atopic eczema, add to references

Evidence	Effect	Remarks
Ref. 3b Case series, n=14 (C)	**Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients** (Heller et al. 2007) Summary: 14 children were treated with MMF after previous treatment with very potent corticosteroids and calcineurin inhibitors. In 4 children the disease cleared, 4 had an excellent response (>90% improvement), 5 had a good response (60-90% improvement) and 1 had an inadequate response (<60% improvement). Doses were titrated until disease clearance or 75 mg/kg/day. Initial response was within 8 weeks (mean 4), maximal effects were achieved after 8-12 weeks (mean 9) at doses of 25-48 mg/kg/day (mean 38). For children 2-8 yrs maximal benefit was achieved at 40-50 mg/kg/day. For children 12-16 yrs at 30-40 mg/kg/day. All doses represented ~1200 mg/m2/day. MMF was well tolerated in all patients. Note: younger children have faster hepatic drug metabolism and therefore require higher doses per body weight. Authors conclude MMF at doses of 30-50 mg/kg/day can be a safe, well-tolerated and effective treatment for severe childhood AD. Monitoring: Full blood count/differential, liver function tests and serum blood urea nitrogen and creatinine levels. Frequency: baseline, after 2 wks, 4 wks followed by monthly or bimonthly. There were no substantial changes in laboratory values in any of the patients.	Indication: atopic dermatitis Age: 2-16 y (mean, 10 y) Dosage: initial 12 – 40 mg/kg/ day in 2 doses. Max. dose 75 mg/kg, total max 3 gram/day. Administration: - Duration: 2 - 24 mo, mean 8 Proposal: Basis for indication atopic eczema, add to references
Ref 3c Case report, n=1 (C)	**Mycophenolate Mofetil and Mood changes in children with skin disorders.** (Arkin, Talasila, and Paller 2016) Summary: 1. Adolescent boy with AD was treated with MMF 500 mg bid. 5 weeks after initiation he developed severe anxiety. His mood changes improved with a few days of MMF discontinuation and resolved within week. There was no recurrence in more than 4 years of follow-up. Complete blood count was normal. 2. Adolescent girl with linear facial morphea was treated with MMF 500 mg bid in combination with MTX 15 mg weekly with folic acid. 8 weeks after initiation she experienced moodiness and anhedonia with declining grades. Within 6 weeks after MMF discontinuation her depressed mood and academic performance normalized. Complete blood count and hepatic function tests were normal.	Indication: severe refractory atopic dermatitis Dosage: 1. 500 mg bid (900 mg/m^2/day), 2. 500 mg bid (850 mg/m^2/day). Duration of treatment: 1. 5 wks, 2. 8 wks. Proposal: Add depression/anxiety to the side effects in children (already mentioned for adults)

Discussion:

Use in the EU and USA for pediatric atopic dermatitis
Most MDs in the USA and Canada considered MMF as second line treatment (30.4%), but 13% of responders also used MMF in the first line. 24.3% only used MMF as a third line drug. The initial dose of MMF was 10 mg/kg/day, titrated up to more than 20 mg/kg/day with a duration of 4-12 months. Use beyond 12 months was often required. When discontinuing treatment, both tapering off the dose in one month and immediate withdrawal were applied. (Totri et al. 2017) Most European MDs do not use MMF for atopic dermatitis (78.3%). (Proudfoot et al. 2013)

Age limits
In Heller et al children from 2 to 16 years were studied. In Waxweiler there was only one 4 year old and the other children were ≥ 11 years.
PROPOSAL: the age limits for atopic dermatitis are 2-18 year old.
MEETING 10-09-2020: approved.

Treatment duration
The initial response to MMF was within 8 weeks (Heller) or 5 weeks (Waxweiler). The total treatment duration different between 2 weeks and 24 months. The mean treatment duration in Heller was 8 months. The Dutch guideline CE mentions data about long term use (> 30 weeks) is sparse. Since there is barely any information about the optimal treatment duration, a recommendation is not possible.
PROPOSAL: use the same phrase as in azathioprine: consider discontinuation of treatment if there is no improvement in the first 3 months of treatment.
MEETING 10-09-2020: approved.

Initial dose and maintenance dose
All guidelines are based on the same case series. (Waxweiler, Agans, and Morrell 2011, Heller et al. 2007). The initial dose differs from 10 – 50 mg/kg and the maintenance dose differs from 20 – 75 mg/kg/day. In Heller et al only one child was titrated up to 75 mg/kg/day, while the overall response was still inadequate. The second highest dose was 48 mg/kg/day in a 2-year old and 6-year old child. The dose of 600 – 1200 mg/m^2 mentioned in the American guideline is comparable to the usual dose in kidney transplant. Presentation of the dose per m^2 would be possible since this takes into account that younger children need higher doses per kg/weight. On the other hand, in dermatology a weight based dose will be more practical.

In Heller, Totri and the European guideline titration to a higher maintenance dose is mentioned, but this titration is not always needed. Based on the data in Heller, a lower initial dose would be advisable. This study describes a 14 year old girl with an initial dose of 25 mg/kg that remained on that dose for 9 months with complete disease clearance. One 6 year old boy started at 40 mg/kg and remained at that dose for 2 months with excellent response. All other children increased the maintenance dose with ~10-20 mg/kg/day. (Heller et al. 2007)
In Waxweiler the dose was not specified: all children were dosed between 20-40 mg/kg/day. The majority of children were ≥ 11 years old. (Waxweiler, Agans, and Morrell 2011)
The American guideline recommends a different initial dose for 'young children' and 'adolescents'. Young children probably means 2-12 year olds and adolescents 12-18 year olds. In Heller et al children ≥ 7 years old already have a lower initial dose (12-28 mg/kg/day). The maintenance doses of the children below 7 years are also slightly higher (40-48 mg/kg/day) then in the older children (25-44 mg/kg/day, non-responder at 75 mg/kg/day excluded).
QUESTION: should there be a higher dose for young children compared to older children? And what should be the cut-off point in ages?
MEETING 10-09-2020: no differentiation in dosing; on the contrary, the starting and maintenance dose will expire, because the boards advises to base the dose on body surface area. Because there is only 1 source mentioning such dose (Sidbury et al. 2014), this dose will be copied. There are no indications how to start or maintain. The remark that younger children need higher dosages will be maintained.
PROPOSAL: 2-18 y old: initial dose 20-40 mg/kg/day, maintenance dose 30-50 mg/kg/day. An initial dose at the upper end of the range is recommended in younger children.
MEETING 10-09-2020: approved.

Dosing frequency
Only Heller mentions the dosing frequency: bid, in 2 doses. Since MMF is also used bid in other indications, this would also be appropriate for atopic dermatitis.
PROPOSAL: daily dose in 2 doses.
MEETING 10-09-2020: approved.

MPA vs. MMF
For MPA there is no evidence and the current NKFK monography is only for MMF (Cellcept and Myfenax©).

PROPOSAL: keep the current NKFK monography only for MMF
MEETING 10-09-2020: approved.

4. Atopic dermatitis - monitoring

Laboratory values to monitor
The values that are often monitored include FBC, creatinine, LFT and TPMT. Electrolytes and urea are measured in some studies.
In Heller et al FBC/diff, LFT, serum blood urea nitrogen and creatinine levels were monitored. The American guidelines recommend monitoring of the same values, except serum blood urea nitrogen. Since this is not described in the Dutch CE guideline as well, urea is not included in the monitoring proposal.

MMF levels are monitored when used after transplantation. All other indications are still 'experimental' and the TDM monography for MMF does not provide information about monitoring in atopic dermatitis. (NVZA 2014) The monography mentions TDM is recommended because of a high variability in pharmacokinetics (10-fold difference in AUC) and because there is a concentration-effect relationship. In none of the studies MMF levels have been measured. As in the other immunosuppressants for AD, I would not propose standard TDM.
PROPOSAL: laboratory values should include FBC/diff, liver function parameters and creatinine.
MEETING 10-09-2020: add: 'At start check for creatinine, liver enzymes (ALAT is sufficient) and complete blood count.'

Standard frequency of monitoring
In Heller et al the frequency of monitoring was at initiation, after 2 weeks, 4 weeks and monthly to bimonthly thereafter. This is comparable to the monitoring recommendations in the American guideline, although they recommend every 2-3 months during maintenance therapy.
In Waxweiler the authors discuss the differences between AZA and MMF in the occurrence of laboratory abnormalities. They carefully conclude MMF seems better tolerated and safer than AZA, although both drugs had similar rates of gastrointestinal complaints. This indicates MMF monitoring should not be more frequent than AZA, maybe even less frequent. In the proposal I included the same frequency as AZA.
PROPOSAL: monitoring before initiation, after 1 month, 2 months and 3 monthly thereafter.
MEETING 10-09-2020: approved.

Abnormal laboratory values: dose adjustment, treatment cessation or additional monitoring
None of the studies or guidelines have recommendations about the interventions if laboratory values are abnormal. Since monitoring intensity is comparable to AZA, the interventions in AZA could be used in MMF as well.
PROPOSAL: use the same recommendations for intervention as in AZA.
MEETING 10-09-2020: approved.

Other recommendations to monitor (comorbidities, vaccinations, contraception)
In the Dutch guideline CE HIV, HBV/HCV should be tested before initiation to rule out active infections. . In the TREAT protocol for MTX it is mentioned that dermatologists in > 30 countries agreed HIV and hepatitis B/C testing is not required for children receiving MTX (Gerbens et al. 2019). This screening should only be performed when there is a history of risk factors. These risk factors are very rare in children.

MMF is contra-indicated during pregnancy. Miscarriages and birth defects have been associated with MMF use during pregnancy. (Service)

PROPOSAL: Patients should be informed about live vaccines and sufficient contraception. Screening for HIV, hepatitis B/C and TB is not recommended.
MEETING 10-09-2020: approved.

Handbook 1 BNF for children 2018-2019	Indication not mentioned	Remarks:
Handbook 2	Indication not mentioned	Remarks:

Pediatric & neonatal dosage handbook 25th edition		
Handbook 3 IBM Micromedex®	No information about atopic dermatitis in paediatrics	Remarks:
Handbook 4 Drug prescribing in renal failure, 5th edition 2007	GFR 30-50: 100% GFR 10-29: no more than 600 mg/m^2/day GFR <10: no more than 600 mg/m^2/day IHD: no more than 600 mg/m^2/day PD: no more than 600 mg/m^2/day CRRT: 100%, monitor serum concentrations when possible, not dialyzable, (D)	Standard dosage: 600 mg/m^2 dose q12h

Additional information:

Renal function:

- Current KF: GFR ≥10 ml/min/1.73m^2: dose adjustment is not indicated.
  GFR <10 ml/min/1.73m2: no recommendation possible
- KNMP: no information
- SmPC: in patients with GFR < 25 ml/min/1,73m^2: avoid doses > 1 gram bid (exception: initial dose after transplantation), for Myfortic, avoid doses > 1440 mg per day.
- Pubmed: no specific information found in monitoring of MMF. A quick search indicates MMF is a good alternative in children with renal dysfunction due to prior use of calcineurin inhibitors.
- Proposal: Keep current KF information

Pharmacogenetics KNMP: no information

Obesity: no information

Proposal meeting (10/09/2020):

Section	Proposal	Results meeting
Dosering - oraal	Age limits: 2-18 y	Approved
Dosering	Startdosering: 20-40 mg/kg/dag	Dosing should be in mg/m2, therefore starting and maintenance dose expires
Dosering	Onderhoudsdosering: 30-50 mg/kg/dag	
Dosering	Een startdosering aan de hoge kant van het doseringsbereik wordt aanbevolen bij jonge kinderen.	Approved
Dosering	Als binnen 3 maanden geen verbetering optreedt, moet worden overwogen mycofenolzuur te staken	Approved
Waarschuwingen en voorzorgen bij kinderen	Add monitoring information:	
Waarschuwingen en voorzorgen bij kinderen	Bij start controle van creatinine, leverenzymen (ALAT voldoende) en volledig bloedbeeld.	Only mention ALAT (not liver enzymes)
Waarschuwingen en voorzorgen bij kinderen	1 maand na start, 2 maanden na start en na elke dosisverhoging opnieuw controle.	Approved
Waarschuwingen en voorzorgen bij kinderen	Vervolgens bij stabiele dosis elke 3 maanden controle (bij niet afwijkende eerdere bevindingen).	Approved
Waarschuwingen en voorzorgen bij kinderen	Bij afwijkende labwaarden gelden de volgende aanbevelingen: • Leverenzymen > 2x normaalwaarde: verlaag dosis en monitor elke 4-6 weken. Bij > 3x normaalwaarde: staak tijdelijk en	Approved

	evalueer bij herstart de laagst mogelijke veilige dosering. • Bij lymfocyten < 1.0x109/L en/of neutrofielen <1.5x109/L: verlaag dosis en overleg eventueel met hematoloog. Monitor wekelijks.	
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan vaccinatie adviezen tijdens mycofenolzuur gebruik.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan adequate anticonceptie/kinderwens. Mycofenolzuur is gecontra-indiceerd tijdens zwangerschap.	Copy from Kompas
Bijwerkingen bij kinderen	Bij kinderen (vooral 12-18 jaar) komt angst en depressie voor.	Approved

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Kinderformularium: Azathioprine

Date literature search: 03-2020 Saved in Pubmed? ☒

1. National registration/guidelines

AD: atopic dermatitis; AZA: azathioprine; CBC: complete blood count; CE: constitutional eczema; diff: differential; DLQI: dermatology quality of life index; EASI: Eczema area and intensity index; HCG: human chorionic gonadotropin; HIV; human immunodeficiency virus; IGA: investigator global assessment; NRS: numeric rating scale; POEM: patient oriented eczema measure; TB: tuberculosis; TPMT: thiopurine methyltransferase

Source	Evidence	Effect	Remarks
Azafalk tabletten, 27-11-2019	SmPC	**4.2** Transplantaties: *kinderen*: startdosis tot max 5 mg/kg, onderhoud 1-4 mg/kg, aanpassen op geleide van klinisch effect en tolerantie Overige toepassingen: *kinderen*: aanvangsdosis 1-3 mg/kg/dag, aanpassen op geleide van klinisch effect en tolerantie NUDT15 Patiënten met het erfelijke gemuteerde NUDT15-gen lopen een verhoogd risico op ernstige toxiciteit door AZA. Voor deze patiënten is doorgaans een dosisvermindering nodig, met name voor patiënten die homozygoot voor de NUDT15-variant zijn. Genotypisch testen op NUDT15-varianten kan worden overwogen voor start van de therapie met AZA. Nauwlettend controleren van het bloedbeeld is in elk geval noodzakelijk.	De dosering bij kinderen is gelijk aan de dosering bij volwassenen. Overige toepassingen: chronisch actieve auto-immuunhepatitis, pemphigus vulgaris, auto-immuunhemolytische anemie en chronische refractaire idiopathische trombocytopenische purpera.
Imuran tabletten, 7-11-2019	SmPC	**4.2** Transplantaties: *kinderen*: startdosis tot max 5 mg/kg, onderhoud 1-4 mg/kg, aanpassen op geleide van klinisch effect en tolerantie Overige toepassingen: *kinderen*: aanvangsdosis 1-3 mg/kg/dag, aanpassen op geleide van klinisch effect en tolerantie Frequentie, type en ernst van bijwerkingen bij kinderen zullen naar verwachting dezelfde zijn als bij volwassenen. Een Amerikaanse studie bij 18 kinderen (3-14 jaar) heeft uitgewezen dat de blootstelling van 6-mercaptopurine 2,4 maal lager was bij kinderen die als te zwaar (boven het 75e percentiel) beschouwd worden. Zij kunnen doseringen aan de hoge kant van het doseringsbereik nodig hebben. Nauwgezette monitoring van de respons wordt aanbevolen.	De dosering bij kinderen is gelijk aan de dosering bij volwassenen. Overige toepassingen: Ernstige reumatoïde artritis, systemische lupus erythematosus, dermatomyositis en polymyositis, chronisch actieve auto-immuunhepatitis, pemphigus vulgaris, polyarteriitis nodosa, auto-immuunhemolytische anemie en chronische refractaire idiopathische trombocytopenische purpera.
National guidelines			
Richtlijn constitutioneel eczeem (NVDV 2019)		Azathioprine (off-label) CE die niet voldoende reageert op lokale therapie: *>2 jaar*: start 50 mg/dag, indien nodig ophogen op geleide van effect en bijwerkingen. Voorafgaand aan de behandeling wordt een TPMT-bepaling aanbevolen. Klinisch effect treedt pas op na 8-12 weken. Tijdens het gebruik van AZA dienen regelmatig controles plaats te vinden op lymfopenie, afname van de nier-, lever-, of beenmergfunctie,	Dosering (kinderen) De aanbevolen dosering van azathioprine bij kinderen is te vinden via het **kinderformularium.** AZA dient voorgeschreven te worden door een specialist in kinderdermatologie. De dosis dient individueel vastgesteld te

Source	Evidence	Effect	Remarks
		ontwikkeling van huidmaligniteiten en monitoring op lymfomen. Monitoring: -Huidinspectie (IGA en controle cutane maligniteit) en jeuk (NRS). Aanvullend kunnen EASI, POEM en DLQI gebruikt worden. - Bloedcontroles:	worden en de laagst mogelijke dosis dient toegepast te worden. Het advies is gebaseerd op Caufield, Waxweiler, Hon, Murphy 2002 en Fuggle.

Tabel 11. Monitoringsschema behandeling met AZA bij CE, bij normale TPMT waarden

Parameter	Bij intake	1 en 2 weken na proef dosering**	Periode in weken			Tijdens onderhouds-dosering (elke 3 mnd.)
			4	8	12	
IGA en NRS jeuk*	x		x	x	x	x
TPMT (optioneel)**	x					
Bloedonderzoek						
Hb, leukocyten, trombocyten	x	x	x	x	x	x
leukocyten differentiatie	x	x	x	x	x	x
ALAT, γ-GT	x	x	x	x	x	x
Serum creatinine	x		x	x	x	x
HIV§**	x					
HBV/HCV§**	x					
Zwangerschap§**	x					

* Aanvullend kunnen de EASI, POEM of DLQI gebruikt worden.
** Bij lage TPMT activiteit: na 1 en 2 weken proefdosering, daarna na 2, 4 en 8 weken, en vervolgens elke 3 maanden. Bij onbekende TPMT geldt hetzelfde schema, maar ook wekelijks gedurende de eerste 2 weken na verhoging van de dosering.
§ Uitsluiten (anamnestisch of testen)
Op indicatie: urinezuur

In het algemeen wordt aanbevolen te starten met een proefdosering van 50 mg/dag. Intensieve controle van bloedbeeld is noodzakelijk. Verhoging van de dosering o.b.v. subjectieve klachten en bloedbeeld. De bepaling van het TPMT (thiopurine methyltransferase)-gehalte voorafgaande aan de behandeling wordt aanbevolen. Toch wordt aanbevolen om bij normale TPMT activiteit de proefdosering van 50 mg aan te houden en blijft intensieve controle van bloedbeeld noodzakelijk.

International guidelines			
Guideline		**Guidelines of care for the management of atopic dermatitis. Section 3.** (Sidbury et al. 2014) <u>Summary (Murphy et al 2002 and Hon 2009)</u> There is literature to support the use of AZA to treat AD for those children whose dermatitis is recalcitrant, or when there is significant psychosocial impact on the patient and family unit. Insufficient data exists to recommend an optimal dose, duration of therapy, or to predict the relapse rate upon discontinuation. TPMT levels should be measured in paediatric patients at baseline, with repeat testing considered in cases of nonresponse or change in response. Evidence shows those children with higher TPMT levels may respond less well to treatment but may have a greater risk of hepatotoxicity*. Similarly, children with lower TPMT levels may have improved clinical response on lower drug doses but may have an increased risk of myelosuppression. * This has been discussed by Murphy et al based on a study in leukemia and inflammatory bowel disease. Monitoring (in general):	Indication: refractory AD Dosage: 1-4 mg/kg/day. Most common dose: 2.5 mg/kg/day.

Source	Evidence	Effect	Remarks
		At baseline: baseline TPMT, renal function, CBC/diff/ platelets, liver function, Hep B and C, TB testing, HIV if indicated, HCG if indicated. Follow-up: renal function, liver function, CBC/diff/ platelets 2x per mo (first 2 mo), monthly (next 4 mo). Then every other mo and with dose increase. HCG if indicated, annual TB testing. Dosing may be guided by TPMT enzyme activity.	
Guideline		**Guidelines of care for the management of atopic dermatitis. Part II.** (Wollenberg et al. 2018) <u>Summary</u> (Caufield et al 2013, Murphy et al 2002 and Hon 2009) • AZA may also be used (off label) in children • Patients should be screened for TPMT activity before starting AZA therapy to reduce the risk for bone marrow toxicity by dose adaptation. The suggested dose range is 1–3 mg/kg/day.	Starting dose children: 25-50 mg/day Maintenance dose children: 2-3 mg/kg/day (TPMT IM 1-1,5 mg/kg/day)

2. Kinetics

- Plasma protein binding: ~20-30% mercaptopurin (IM)
- Metabolism: Highly converted to mercaptopurin and nitromethylimidazole during first liver passage. Other metabolites include iosinic acid and 6-thiourinic acid (inactive).
  Mercaptopurin is converted to 6-TIMP, which is converted by TPMT to methylated metabolites. One of these metabolites (monophosphate 6-MTIMP) is associated with myelotoxicity. 6-TIMP is also converted by IMPDH to 6-TGN.
- Excretion: Oral dose: ~50% is renally excreted with 24 h (predominantly metabolites) and ~12% is excreted by feces.
- TDM (NVZA): 6-TGN: 300-600 pmol/8*10^8 RBC (therapeutic), > 600 (toxic). 6-MMP/6-TGN ratio: < 20 (therapeutic). 6-MMP: > 5700 pmol/8*10^8 RBC (toxic). Based on Dervieux & Boulieu method of analysis. Lennard to Dervieux: 1.2 – 1.4 fold difference.

3. Atopic dermatitis

Articles regarding use of oral AZA in severe, refractory atopic dermatitis in paediatric patients are summarized in the table below. All studies are observational unless stated otherwise.

Study	Age	Initial dose (per day)	Treatment dose (per day)	Outcome	Time to initial response	Duration
(Murphy and Atherton 2002) N=48 retrospective	38-198 mo	2.0-3.5 mg/kg.	Increased to ~ 3.0 mg /kg in 14 pts due to insufficient response	After 3 mo 28 pts were excellent responders (> 90% improvement), 13 good responders (60-90% improvement) and 7 poor responders (<60% improvement) The authors conclude therapy can be initiated at 2.5-3.5 mg/kg if TPMT levels are normal.	Mean 4 wks (2-6 wks)	Unknown only assessment after 3 mo
(Hon et al. 2009) N=17 retrospective	Mean 16.1 y (9.3 – 22 y)	0.5 mg/kg to nearest 25 mg tablet, ↑ every 1-2 wk	1.2-3.5 mg/kg	After 3 mo and 6 mo a significant decrease in (objective) SCORAD, % of affected skin and pruritis. At 6 mo, females had significant more improvement than males. One patient discontinued AZA treatment after 4 mo due to lack of efficacy.	Generally within 3 mo	Unknown Study duration was 6 mo
(Waxweiler, Agans, and Morrell 2011) N=28 Case series	Mean 11.4 y (3-17 y)	< 1 mg/kg	TPMT EM: dose ↑ to 3 mg/kg TPMT IM: dose 1 mg/kg	In 17 children symptoms improved, 6 children had some improvement and 5 children did not improve. 12 patients switched to MMF because of side effects and/or treatment failure.	Mean 5.3 wks (in responders)	Mean 14.9 mo (1-40 mo)
(Caufield and Tom 2013) N=12 prospective	Median 9 y (start) (2.6-18.1 y)	2.5 mg/kg (normal TPMT), 2-2.5 mg/kg (TPMT 11.9-15.3 U/mL), 1 mg/kg (TPMT IM)	1.25-3.4 mg/kg Dose ↑ 0.5 mg /kg in normal and 11.9-15.3 U/mL TPMT, 0.25 mg/kg in TPMT IM	11 of 12 patients experienced significant improvement. In 3 pts TPMT levels shifted between categories during therapy: - 2 pt improved while shifting from normal to possible carrier (1.9-15.3 u/mL.1 pt used 3 mg/kg since without adverse effects. - 1 pt worsened while shifting from IM to normal. Dose ↑ to 3 mg/kg did not improve response, so treatment was terminated after 15 mo.	Unknown (infrequent assessment effect)	~ 8-16.5 mo (estimation, some pts were still tapering off)
(Fuggle et al. 2015) N=82 Prospective	Mean 8.3 y (start) (SEM 0.4)	2.0-2.5 mg/kg (normal TPMT), 1-1.5 mg/kg (TPMT IM)	2.0-3.5 mg/kg	Study did not measure efficacy	-	Mean 2.14 y
(Noguera-Morel et al. 2019) N=11 retrospective	Mean 13 y (8-18 y)	Mean 1.8 mg/kg/day	Not described Mean TPMT levels: 19.8 IU/ mL 13.8-18 U/mL was treated with 1.5 mg/kg, 18.1-26.0 U with 2.5 mg/kg	After 4 wks none of the pts were excellent responders (≥ 90% improvement). After 3-4 months 4 pts were excellent responders, 3 good responders (50-89% improvement) and 2 poor responders (<50% improvement). After 6 mo 2 out of 3 good responders became excellent responders. After complete follow-up (mean 33.1 mo) 7 patients were excellent responders.	Somewhere between 4 wks and 3-4 mo.	Mean 10.8 mo
(Yee and Orchard 2018) N=95 retrospective	Mean 10.6 y (2-18 y)	3 wks: 1/3 dose 3 wks: 2/3 dose	After 6 wks: 2.5 mg/kg (if no issues)	Study did not measure efficacy	-	Mean 656 d (4 d – 70 mo)

SCORAD: SCORing Atopic Dermatitis; TPMT: thiopurine methyltransferase

Initial: MvR Checked: MdH Meeting: 10-9-2020

Discussion:

Use in EU and USA for pediatric atopic dermatitis

Most MDs in Europe considered AZA as second line treatment (28.7%), but 21.7% of responders also used AZA in the first line. 20.5% only used AZA as a third line drug (and 29.1% did not use AZA at all). The initial dose of AZA was ~ 1 mg/kg/day, titrated up to max. 3 mg/kg/day with a duration of 4-12 months. Use beyond 12 months was often required. When discontinuing treatment, both tapering off the dose in one month and immediate withdrawal were applied. (Proudfoot et al. 2013) In the US and Canada AZA was most often considered third line treatment (33%). Their initial dose was usually 2 mg/kg/day with a maximum of 3 mg/kg/day. Average and maximum duration of treatment and regimen to discontinue treatment were comparable to European MDs. (Totri et al. 2017)

Age limits

In most studies the range of ages has a lower limit of 3 years or above. Some studies mention 2 year olds as the youngest included patients. (Caufield and Tom 2013, Yee and Orchard 2018). The Dutch guideline Constitutional eczema mentions 2 year as the lower limit. The NKFK currently also mentions 1 month as lower limit for the indication auto-immune diseases, but this is not supported by the literature about atopic dermatitis.
PROPOSAL: the age limits for atopic dermatitis are 2-18 year old.
MEETING 10-09-2020: approved.

Treatment duration

Treatment duration differs, but is usually more than 6 months. In one prospective study the mean duration in 82 children was over 2 years. In retrospective studies treatment duration can be up to 70 months (almost 6 years). (Yee and Orchard 2018) The Dutch guideline Constitutional eczema does not recommend a treatment duration (NVDV 2019).

Minimum duration of therapy is set to 12 months for inflammatory bowel disease in the current KF monograph, since the first 3-4 months a clinical effect is not expected. In Waxweiler et al some responders already tapered down treatment after 3 months, but most responders were treated for 12 months or longer. (Waxweiler, Agans, and Morrell 2011) Initial improvement was at week 9 at the latest. This would be in accordance with the current recommendation in the KF monograph: other diseases: if there is no improvement in the first 3 months of treatment, consider discontinuation of AZA.
PROPOSAL: an optimal or maximum treatment duration cannot be provided. The information from auto-immune diseases in NKFK regarding evaluation time and minimum treatment duration can also be used for AD.
MEETING 10-09-2020: change to 'If no improvement occurs within 3 months with the highest dose tolerated, discontinuation of azathioprine should be considered.'.

Initial dose

If TPMT is unknown, most studies have a low initial dose and increase the dose based on clinical response and toxicity. If TPMT was unknown at the time of initiation, a dose of 0.5 - 1 mg/kg was used. (Hon et al. 2009, Waxweiler, Agans, and Morrell 2011). If TPMT activity was known to be normal, initial doses were usually between 2 - 3.5 mg/kg. (Murphy and Atherton 2002). For TPMT intermediate metabolizers (IM), in 2 children 1 - 1.25 mg/kg/day has been

successfully used. (Murphy and Atherton 2003). Other studies also use doses of 1 – 1.5 mg/kg/day, depending on the definition of IM (heterozygous) and a category between IM and normal, a possible heterozygous. (Noguera-Morel et al. 2019, Caufield and Tom 2013, Waxweiler, Agans, and Morrell 2011).
In auto-immune diseases in the NKFK, there is no distinction between the initial dose and the maintenance dose. It seems like the only reason for making a distinction between these doses, is the uncertainty about TPMT activity.

Test dose
The Dutch guidelines CE mentions a test dose should be used for the first 2 weeks. (NVDV 2019) During this time, extra monitoring is recommended. For other indications a test dose is not described. (KNMP 2020)

QUESTION: the main question here is about TPMT genotyping. If the NKFK recommends genotyping, a test dose or a low initial dose is not necessary. If the guideline CE as described for adults is also applicable for children, a test dose might be useful. (see general question on p. 1)
PROPOSAL: only provide one dose: a separate initial or test dose is not indicated.
MEETING 10-09-2020: approved.

Maintenance dose
Not all studies provide a mean treatment dose: some only mention a protocol dose or an initial dose. (Yee and Orchard 2018, Noguera-Morel et al. 2019)
The treatment doses in 2 studies varied between 1.2 and 3.5 mg/kg/day. (Hon et al. 2009, Caufield and Tom 2013). The low doses are probably used by children with low TPMT activity, since these studies used doses of 1 mg/kg/day in TPMT IM. In Waxweiler et al children with normal TPMT were up titrated to 3 mg/kg/day. In 25% of these children the dose was reduced afterwards. (Waxweiler, Agans, and Morrell 2011) So standard up titration is probably not necessary.
The studies do not mention if the daily dose was once daily or in divided doses. The guideline CE does not specify the dosing regimen. (NVDV 2019) Other indications mention dosing is possible in 1 or more doses. (KNMP 2020)
PROPOSAL: 1-3 mg/kg/day for atopic dermatitis. In patients with low TPMT activity doses around 1-1.5 mg/kg/day are usually sufficient. In patients with normal TPMT 3.5 mg/kg/day has also been described. If a frequency is preferred, this would be in 1 or more doses.
MEETING 10-09-2020: approved, frequency should be once daily.

4. Atopic dermatitis - monitoring

The articles in table 1 are also checked for information about monitoring of laboratory values. If the article provides specific recommendations, this is provided in the discussion.

Study	Excl criteria related to monitoring/ TPMT	Monitoring	Frequency of monitoring	Participants with lab abnormalities	Treatment alterations	Side effects in general
(Murphy and Atherton 2002) n=48	Abnormal TPMT levels (normal range 8-14.5	FBC/diff, UEC, LFT	4 wks, 12 wks and 12 weekly after initiation (more	No pts with neutropenia 15 pt: transient lymphopenia (never < $1.5*10^9$/L)	1 pt with abnormalities in LFTs terminated treat-ment. The authors men-tion the abnormality was	1 pt had nausea, vomiting and diarrhoea, relieved by dose reduction. 1 pt may have had a hypersensitivity

	nmol.h.mL RBC)		frequent if dose is increased).	1 pt: transient and minor thrombocytopenia. 5 pt: transient abnormalities in LFTs.	mild and termination was not necessary. Others returned to normal without interventions.	reaction that resolved after treatment termination. Other clinical side effects not described.
(Hon et al. 2009) N=17	TPMT not measured	FBC, LFT	Weekly until the target dosage was reached, then 4–6 weekly.	None	-	No severe hypersensitivity or increased susceptibility to cutaneous viral infections was observed.
(Waxweiler, Agans, and Morrell 2011) N=28	Not mentioned	Not specified	Not specified	7 pt with lab abnormalities (abnormal liver function test (n=6), low haemoglobin or abnormal white blood cell count). Mild abnormalities are not described.	Dose adjustment was needed in all pts.	Most common (n=8) GI complains. 16 pts had a cutaneous infection.
(Caufield and Tom 2013) N=12	TPMT levels ≤ 5.9 U/mL, impaired hepatic or renal function	Laboratory monitoring. TPMT, 6-TGN and 6-MMP measured if: treatment is stable (just before tapering off), inadequate response or change in response.	At screening, 2 wks, 4 wks, 8 wks and 12 wks, every 4-8 wks thereafter	1 pt: Absolute neutrophile count of 1291/mm^3 at mo 4 1 pt: mildly elevated serum transaminases 6-TGN levels in 11 respon-ders were between 45-358 pmol/8*10^8 RBC.	Neutrophile counts normalized in subsequent monitoring. Pt with elevated transaminases reduced dose from 2.5 to 1.75 mg/kg/day successful.	No patients ceased treatment due to adverse events. 2 pts had minor GI upset for a few wks. TPMT levels did not correlate with GI or other side effects.
(Fuggle et al. 2015) N=82	Unknown TPMT Undetec-table TPMT levels	FBC, and LFT TPMT level, vitamin D, VZV, hep. B and C, HIV, HHV-8, Mantoux at screening.	At screening, after 1 wk, 3 wks, 7 wks and every 3 mo	33 pts with lab abnormalities: 18/33 pts were pronounced. 8 pts: CBC abnormalities (lymphocytes ≤ 0.5*10^9/L (n=1), or neutrophils <1.0 × 10^9/L (n=7). 11 pts: ↑ hepatic transamina-ses (levels > 50 U/L) 11 patients had low levels of TPMT. Being a TPMT carrier did not affect the OR of having an adverse event or changed blood indices.	5/8 pts: monitoring 2/8 pts: brief cessation 1/8: dose reduction 1/8: treatment termination due to recurrent neutropenia 5/11: monitoring 4/11: brief cessation 1/11: dose reduction 1/11: treatment termination due to recurrent elevation.	20% had clinical adverse effects, generally mild. 3 pts ceased treatment after clinical adverse events (headache, recurrent herpes liabilis and recurrent airway infection)
(Noguera-Morel et al. 2019) N=11	TPMT levels < 5.1 U/mL in red cells	FBC and biochemistry	At screening, after 15 d, after 4 wks and every 3 mo.	1 pt: increased transaminases	None	2 patients ceased treatment due to epigastric pain (in first mo, resolved after discontinuation).
(Yee and Orchard 2018) N=95	-	FBC, UEC, LFT TPMT and IgE at initiation	At screening, after 1 mo, after 2 mo and every 3 mo.	12 pt: lymphopenia (lymphocytes < 1.0*10^9/L) 4 pt: elevated hepatic trans-aminase 4 pt: neutropenia 1 pt: thrombocytopenia,	3 pt terminated treatment (2 pts ↑ hepatic transaminase (mean AST 62.5 U/L and mean ALT 65 U/L) without side effects and 1 pt with AST	13 pt with clinical side effects. 7 pt terminated treatment due to side effects (3 pts with nausea, vomiting and single cases of infection, rash,

				1 pt: anemia,	62 U/L and ALT 52 U/L and drug hypersensitivity)	headache and hypersensitivity).

6-MMP: 6-methylmercaptopurine; 6-TGN: 6-thioguanine nucleotide; FBC: full blood count, HHV: human herpesvirus; UEC: electrolytes, urea and creatinine, LFT: liver function test, Cr: creatinine; RBC: red blood cells; ULN: upper limit of normal; TB: tuberculosis; TPMT: thiopurine-S-methyltransferase; VZV: varicella zoster virus

Discussion:

Laboratory values to monitor

The values that are often monitored include FBC, creatinine, LFT and TPMT. Electrolytes and urea are measured in some studies. The guideline Constitutional Eczema (CE) 2019 recommends to monitor hemoglobin, leucocytes, thrombocytes, leucocytes differentiation, ALAT, γGT and serum creatinine. Uric acid is also recommended upon request. TPMT is optional: if the activity is not measured, extra monitoring is required. (NVDV 2019)
In the Dutch guideline JIA monitoring for MTX in pediatrics is described. (NVK 2018) This could be the basis of the monitoring recommendations in AZA.

AZA levels are monitored in Crohn's disease and ulcerative colitis by determination of 6-TGN and 6-MMP/6-TGN ratio. (NVZA 2018) In one study 6-TGN (effectivity) and 6-MMP (toxicity) are measured. They conclude the levels did not correspond with clinical response and are not helpful in AD treatment monitoring. (Caufield and Tom 2013) Other studies do not measure 6-TGN and/or 6-MMP.
PROPOSAL: laboratory values should be based on the majority of studies in pediatric atopic dermatitis and monitoring recommendations for MTX in JIA in the Netherlands.
MEETING 10-09-2020: approved.

Standard frequency of monitoring

The frequency of monitoring is not always described and dependent on study duration. The study of Yee et al focused on the monitoring of AZA in pediatric dermatology in Australia. They conclude less frequent monitoring did not result in any significant adverse events over a 15-year period. They monitored before initiation of therapy, after 1 month and after 2 months followed by monitoring every 3 months. All laboratory values were determined at these time points, while the Dutch guideline states all laboratory values should be monitored before initiation, after 4 weeks, 8 weeks and 12 weeks and every 3 months. Extra monitoring is required if TPMT activity is low or unknown. A test dose is used in the first 2 weeks, followed by monitoring of all values except serum creatinine.
PROPOSAL: monitoring before initiation, after 1 month, 2 months and 3 monthly thereafter.
MEETING 10-09-2020: approved.

TPMT

The Dutch Pharmacogenetics Working Group of the KNMP (Royal Dutch Pharmacists Association) has provided guidelines about pre-emptive genotyping for TPMT and AZA. They conclude genotyping is essential. (KNMP 2019) This recommendation is mainly based on studies with adults, but also includes some studies in children. On the other hand, Caufield mentions one patient with intermediate TPMT activity at baseline was genotyped and did not carry one of the known TPMT variants (*2, *3A, *3B and *3C). (Caufield and Tom 2013) Other studies only mention TPMT levels (phenotype) and not the genotype.

In the PgGx monography AZA, TPMT activity is mentioned to be higher in children than in adults. Also, the correlation between genotype and phenotype is usually good, although the lowest correlation is found in intermediate metabolizers. (as illustrated by Caufield). The NVZA working group prefers genotyping since this is more practical and less expensive. (NVZA 2017)

QUESTION: should TPMT genotyping or phenotyping be obligatory instead of optional? And if TPMT activity is normal, is a test dose and intensive monitoring still indicated? (page 157 of guideline CE. Table 11 on page 156 states this is only the case in unknown or low TPMT activity.) (see general question on p. 1)
PROPOSAL: recommend TPMT genotyping and refer to the KNMP dosing guidelines for TPMT variants.
MEETING 10-09-2020: approved.

NUDT15
NUDT15 genotyping is not mentioned in any of the studies, but it is mentioned in the SmPC. The Dutch Pharmacogenetics Working Group of the KNMP has provided dose reductions for NUDT15 variants comparable to TPMT. Pre-emptive genotyping is also essential. If both NUDT15 and TPMT have a poor metabolizer status, the risk of toxicity further increases.
QUESTION: should NUDT15 also be mentioned? With the same warnings as TPMT? (see general question on p. 1)
MEETING 10-09-2020: yes.

Abnormal laboratory values: dose adjustment, treatment cessation or additional monitoring
Only study provides concrete dose recommendations: (Fuggle et al. 2015)

- 1st breach in blood parameters: retest in 1 week
- If normal findings: no treatment alterations, if still breached: stop AZA for 1 week and retest.
- If normal findings: restart AZA at lower dose (0.25 mg/kg reduction in TPMT EM and 0.25-0.5 mg/kg if TPMT IM).
- If still breached: clinical evaluation if AZA should be continued.
- If the dose is adjusted or there is a breach in parameters: standard monitoring cycle.

Caufield also mentions one patient with elevated transaminases in whom the dose was reduced from 2.5 to 1.75 mg/kg/day. Treatment could be continued with normalized transaminases. (Caufield and Tom 2013)

The above-mentioned protocol is applicable for both FBC and liver transaminases. (Fuggle et al. 2015) They also provide specific cut-off values for pronounced abnormalities: lymphocytes ≤ $0.5*10^9$/L, neutrophils <1.0×10^9/L and hepatic transaminases (levels > 50 U/L). The neutrophil cut-off is low compared to the TREAT protocol for MTX and CsA (see monography CsA). (Irvine et al. 2018) Significant changes in hepatic transaminases are often defined as the upper limit of normal, which is usually 2-3 times. The study by Fuggle et al also recommends to change the absolute value of 50 U/L to an increase of more than twice the upper limit of the normal range for age. (Fuggle et al. 2015)
In the study by Yee et al lymphocytes ≤ $1.0*10^9$/L are considered as a marker for toxicity. Dose increases are possible if lymphocytes > $1.7*10^9$/L.(Yee and Orchard 2018). The cut-off values in Fuggle et al are probably lower than usual, since they make a distinction between 'adverse events' (cut off neutrophils

and lymphocytes the same as the TREAT protocol and Yee et al) and 'pronounced adverse events'. But even in their pronounced adverse event definition, about half the patients returned to normal without intervention (only more intensive monitoring).

QUESTION: what should be the recommendations for lymphocyte count and neutrophil count? (cut-off and action)
PROPOSAL: The recommendation for LFT should be based on the JIA guideline. The recommendation for lymphocyte and neutrophil abnormalities can be based on Fuggle. The current proposal is adopted from the recommendations from CsA (with higher cut-off values and dose reduction).
MEETING 10-09-2020: approved.

Other recommendations to monitor (comorbidities, vaccinations, contraception)
In the Dutch guideline CE HIV, HBV/HCV should be tested before initiation to rule out active infections. In the TREAT protocol for MTX it is mentioned that dermatologists in > 30 countries agreed HIV and hepatitis B/C testing is not required for children receiving MTX (Gerbens et al. 2019). This screening should only be performed when there is a history of risk factors. These risk factors are very rare in children.

PROPOSAL: Screening for HIV and hepatitis B/C is not recommended. Patients should be informed about live vaccines and sufficient contraception. AZA can have effects on the fetus, but can be used during pregnancy if necessary. (Teratology Information Centre)
MEETING 10-09-2020: approved.

Handbook 1 BNF for children 2018-2019	Indication not mentioned	Remarks:
Handbook 2 Pediatric & neonatal dosage handbook 25th edition	Indication not mentioned	Remarks:
Handbook 3 IBM Micromedex®	Atopic dermatitis (oral:) Non FDA use: Pediatric, Class IIb, Category C Two pediatric patients partially deficient in thiopurine methyltransferase (TMPT) received successful azathioprine therapy with azathioprine dose reductions without significant myelosuppression. Thiopurine methyltransferase (TMPT) level is a good predictor of pediatric patients unlikely to develop myelosuppression to azathioprine therapy in children with atopic eczema, thereby increasing the likelihood of a positive clinical response.	Remarks: Dose: 1.25 mg/kg (14 year old) and 1 mg/kg (7 year old). Both TPMT IM. Effective dose according to authors: 2,5 – 3,5 mg/kg in patients with normal TPMT
Handbook 4 Drug prescribing in renal failure, 5th edition 2007	GFR 30-50: 75% q24h GFR 10-29: 75% q24h GFR <10: 50%q24h IHD: 50%q24h PD: 50%q24h CRRT: 75%q24h (D)	Standard dosage: 2-5 mg/kg/day q24h, then 1-3 mg/kg/day q24h depending upon condition being treated

Additional information:
Renal function:
- Current KF: no data about dose adjustments in renal dysfunction
- KNMP: dose as in normal renal function.
- SmPC: dose at lower limit within normal therapeutic range (Azafalk). Decrease initial dose (Imuran)
- Pubmed: see monitoring table
- Proposal: no specific proposal for renal dysfunction.

Pharmacogenetics KNMP: **TPMT & NUDT15**

Bij thiopurinemethyltransferase (**TPMT**) genvariaties:
-poor metabolizers: de intracellulaire concentratie van de actieve metaboliet kan verhoogd zijn, een alternatief of (start)dosisverlaging tot 10% van de standaarddosering wordt aanbevolen;
-intermediate metabolizers: de intracellulaire concentratie van de actieve metaboliet kan verhoogd zijn, (start)dosisverlaging tot 50% van de standaarddosering wordt aanbevolen, bij doseringen tot 1.5 mg/kg lich.gewicht per dag is dosisaanpassing niet nodig.

Bij Nudixhydrolase 15 (**NUDT15**) genvariaties:
-poor metabolizers: de intracellulaire concentratie van de actieve metaboliet kan verhoogd zijn, een alternatief of (start)dosisverlaging tot 10% van de standaarddosering wordt aanbevolen;
-intermediate metabolizers: de intracellulaire concentratie van de actieve metaboliet kan verhoogd zijn, (start)dosisverlaging tot 50% van de standaarddosering wordt aanbevolen.

Obesity: no information

Proposal meeting (10/09/2020):

Section	Proposal	Results meeting
Dosering	Age limits: 2-18 y	Approved
Dosering	1-3 mg/kg/dag in 1 dosis (of in meerdere doses).	Approved, although the more frequent dosing is removed (only once daily). Add to

		consider genotyping, referring to warnings&precautions
Dosering	Behandelduur: een behandelingsduur van ten minste 12 maanden moet worden overwogen omdat een klinisch effect niet binnen 3-4 maanden te verwachten is. Als binnen 3 maanden geen verbetering optreedt, moet worden overwogen azathioprine te staken	Change to: Als binnen 3 maanden geen verbetering optreedt met de hoogste dosis die verdragen wordt, moet worden overwogen azathioprine te staken
Waarschuwingen en voorzorgen bij kinderen	Standaard zin over farmacogenetica	Approved
Waarschuwingen en voorzorgen bij kinderen	Add monitoring information:	
Waarschuwingen en voorzorgen bij kinderen	Bij start controle van creatinine, leverenzymen (ALAT voldoende) en volledig bloedbeeld.	Approved, only ALAT, not liver enzymes
Waarschuwingen en voorzorgen bij kinderen	Bepaal het TPMT genotype. Bij TPMT PM of IM, zie adviezen KNMP werkgroep voor dosisaanbevelingen.	Add NUDT15 recommendation, add link to website
Waarschuwingen en voorzorgen bij kinderen	1 maand na start, 2 maanden na start en na elke dosisverhoging opnieuw controle.	Extra monitoring when no genotyping is done; 1 week after start and after each dose adjustment
Waarschuwingen en voorzorgen bij kinderen	Vervolgens bij stabiele dosis elke 3 maanden controle (bij niet afwijkende eerdere bevindingen).	Approved
Waarschuwingen en voorzorgen bij kinderen	Bij afwijkende labwaarden gelden de volgende aanbevelingen: • Leverenzymen > 2x normaalwaarde: verlaag dosis en monitor elke 4-6 weken. Bij > 3x normaalwaarde: staak tijdelijk en evalueer bij herstart de laagst mogelijke veilige dosering. • Bij lymfocyten < 1.0x109/L en/of neutrofielen <1.5x109/L: verlaag dosis en overleg eventueel met hematoloog. Monitor wekelijks.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan vaccinatie adviezen tijdens azathioprine gebruik.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan adequate anticonceptie/kinderwens. Azathioprine kan indien noodzakelijk gebruikt worden tijdens zwangerschap, maar extra controle van de pasgeborene is nodig.	Insert contraceptive recommendations according to Farmacotherapeutisch Kompas

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Kinderformularium: prednisolone

Date literature search: 07-2020 Saved in Pubmed? ☐

1. National registration/guidelines

AD: atopic dermatitis; AZA: azathioprine; CE: constitutional eczema; OCS: oral corticosteroids; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MTX: methotrexate

Source	Evidence	Effect	Remarks
Ref. 1a Prednisolon tabletten 29-08-2017	SmPC	**4.2** Dermatologische aandoeningen: Geen specifieke dosering of vermelding van kinderen. **4.4** Bij kinderen is bijzondere aandacht vereist ter voorkoming van de groeiremming. Daarom wordt bij kinderen, meer nog dan bij volwassenen, gestreefd naar een alternerende dosering.	
National guidelines			
Richtlijn constitutioneel eczeem (NVDV 2019)		<u>Orale corticosteroïden (OCS)</u> CE die niet voldoende reageert op lokale therapie: *>2 jaar*: continu of chronisch intermitterend gebruik van OCS wordt afgeraden. Kortdurende toepassing (2-3 weken) bij exacerbaties van CE of als overbruggende therapie naar een traag werkend niet-steroïde immunomodulerend middel (behandeleffect na 8-12 weken), zoals AZA, MMF/MPA, MTX bij ernstig, snel progressief of invaliderend CE kan overwogen worden. OCS zijn effectief, maar door het bijwerkingenprofiel kan beter andere systemische medicatie toegepast worden. Bij kinderen kunnen OCS ook overwogen worden, als deze ook gewenst/geïndiceerd zijn voor het behandelen van co-morbiditeit (bijv. astma exacerbaties). Kinderen die langdurig OCS gebruiken, kunnen 'booster' vaccinatieprotocollen nodig hebben [Sidbury 2014]; medebehandeling door de kinderarts is hierbij gewenst. <u>Monitoring</u> *Kortdurend:* uitgebreide monitoring is niet zinvol. Bij (bestaande) diabetes mellitus is monitoring van de bloedglucosewaarde wel zinvol. *Langdurig:* geef osteoporoseprofylaxe. Controle van bloeddruk, oogonderzoek, hypothalamus-hypofyse-bijnier as suppressietesten, botdichtheid metingen en groeimetingen (kinderen) kunnen nodig zijn.	<u>Dosering (kinderen)</u> De aanbevolen dosering van orale corticosteroïden bij kinderen is te vinden via het **kinderformularium**. OCS dienen voorgeschreven te worden door een specialist in kinderdermatologie. De dosis dient individueel vastgesteld te worden en de laagst mogelijke dosis dient toegepast te worden. Het advies is gebaseerd op Heddle en La Rosa (OCS: beclomethason en flunisolide)
International guidelines			
Guideline		**Guidelines of care for the management of atopic dermatitis. Section 3.** (Sidbury et al. 2014) <u>Summary (no references for children)</u> Systemic steroids (oral or parenteral) should generally be avoided in adults and children with AD because the potential short-term and long-term adverse effects, described below, largely outweigh the benefits. Systemic steroids may be considered for short-term use	Indication: refractory AD General dose: 0.5-1.0 mg/kg. Dose tapering is indicated to decrease the risk of adrenal suppression.

Source	Evidence	Effect	Remarks
		in individual cases while other systemic or phototherapy regimens are being initiated and/or optimized. Children and adolescents given systemic steroids can experience decreased linear growth. Monitoring: Patients on long-term OCS may require blood pressure monitoring, ophthalmologic examination, hypothalamic-pituitary-adrenal axis suppression testing and growth-velocity measurement (children).	
Guideline		**Guidelines of care for the management of atopic dermatitis. Part II.** (Wollenberg et al. 2018) <u>Summary</u> (based on Schmitt (adults) • Short-term (up to 1 week) treatment with OCS may be an option to treat an acute flare in exceptional cases of AE. Restrictive use, largely limited to adult patients with severe AE, is recommended. • The daily dose should be adjusted to and not exceed 0.5 mg/kg bodyweight. • Long-term use of OCS in AE patients is not recommended. The indication for oral steroids in children should be handled even more cautiously than in adults.	Starting dose children: 0.2-0.5 mg/kg/day Not for maintenance

2. Kinetics

- Plasma protein binding: ~60-70% (IM)
- Metabolism: hepatic metabolism to sulphate- and glucuronide conjugates
- Excretion: renal excretion of metabolites
- TDM (NVZA): -

3. Atopic dermatitis

ACTH: adrenocorticope hormone; AD: atopic dermatitis; CE: constitutional eczema; OCS: oral corticosteroids;

Evidence	Effect	Remarks
Ref. 3a Case series, n=5 (C)	**Treatment with ACTH and cortisone of atopic dermatitis (eczema) in infants and children** (Glaser 1952) <u>Summary:</u> 1 pt with depression was treated with cortisone for 29 days with a total dose of 4050 mg (IM). She relapsed after 3 weeks and was treated for 21 days with 1860 mg cortisone (1060 mg IM, 800 mg oral). She continued oral cortisone after the second treatment course and discontinued later on. Within 2 weeks she relapsed again. A strict diet eventually improved her condition. 4 pts were treated with ACTH (6-23 mo) with doses around 2.5-10 mg every 6 h. The authors conclude the effect of ACTH and cortisone in AD is comparable. Cortisone should be tried if the Thorn test is negative. Side effects in ACTH cases included hypertension (subsided after dose reduction) and mild nephrosis. Depression was not considered a contra-indication for cortisone therapy: the depression subsided every time the eczema cleared (the first 2 times while on cortisone therapy).	Indication: severe AD Age: 14 y CS: cortisone Dosage: ~118 mg/day Administration: IM + oral Duration: 3 d <u>Proposal:</u> Basis for indication AD, add to references.

Evidence	Effect	Remarks
Ref. 3b Case series, n=15 (C)	**Infantile eczema treated with oral cortisone** (Solomons 1954) Summary: 6 pts had a poor response at doses between 75-87.5 mg/day. One 2 y old developed toxicity: rounding of the face and increase of the scalp of eyebrow hair. 3-4 mo after discontinuation of cortisone the toxicity was almost gone. 6 pts had a moderate response at doses between 25-75 m/day. 1 pt had a relapse after 9 mo, treated with cortisone 75 mg/day for 1 mo. The dose was gradually decreased in 6 weeks. Pts were treated for 1.5-5 mo with follow up after 3-10 mo. All pts experienced mild symptoms at follow up, 1 pt had 2 mild recurrences treated with local treatment. 3 pts had a good response at doses between 25-75 mg daily. Pts were treated for 1-4 mo with follow up after 1-6 mo. None of the patients relapsed. 2 pts had severe hay-fever, which has been described to be a predictor for good response to cortisone.	Indication: severe AD Age: 0.5-3 y CS: cortisone Dosage: initial dose: 50-75 mg (used for 1.5-2 weeks), maintenance dose 25-87.5 mg/day. Administration: unknown Duration: 1-5 mo in moderate – good responders. NOTE: maintenance doses were 25-50 mg in moderate-good responders. Proposal: Basis for indication AD, add to references.
Ref. 3c Double-blind cross-over trial, n=26 (B)	**Combined oral and nasal beclomethasone diproprionate in children with atopic eczema: a randomized controlled trial** (Heddle et al. 1984) Summary: The pts started with 4 weeks beclomethasone or placebo, 4 weeks wash-out, followed by 4 weeks in the other treatment arm. Mean severity of AD decreased (redness, surface damage, lichenification, no of zones affected and parental judgement on daytime itch and antihistamine use). No severe adverse effects were reported. The 24 h free cortisol excretion was not significantly altered (only 3 values below 95% CI), meaning the adrenal suppression is small after 4 wks of treatment. NB: the therapy schedule is very unusual (caps for inhalation were diluted and administered orally).	Indication: moderate-to-severe refractory AD Age: 3-14 y (mean 6.5 y) CS: beclomethasone diproprionate Dosage: 200 µg (+ 50 µg aerosole) both 4 times daily Administration: oral (dissolved in 20 mL water) + nasal Duration: 4 wks Proposal: -
Ref. 3d Case, n=14 (C)	**The treatment of difficult atopic dermatitis in childhood with oral beclomethasone dipropionate** (Aylett, Atherton, and Preece 1992) (abstract only) Summary: 14/15 pt demonstrated substantial benefit. 10/14 pt reached maintenance dosing without reflaring (mean dose: 1000 µg/day (range 800-1800 µg/day)). At this maintenance dose, there was evidence of deceleration of linear growth in 7/10 patients. There was no difference between 8 a.m. plasma cortisol levels and those on the maintenance dose. The 24-hour urinary cortisol excretion was reduced during maintenance, but not significant. The authors conclude oral beclomethasone is a useful treatment in widespread childhood atopic AD that has not responded adequately to topical therapy. However, it is mandatory that growth should be monitored carefully during its use.	Indication: severe AD Age: unknown CS: beclomethasone dipropionate Dosage: 600 µg 3x per day Administration: oral Duration: 4 wks, then tapered to maintenance dose Proposal: -
Ref. 3e Case, n=1 (C)	**Do some patients with atopic dermatitis require long-term oral steroid therapy?** (Sonenthal, Grammer, and Patterson 1993) Summary:	Indication: severe AD Age: 7 y CS: prednisone Dosage: 5 mg qod Administration: oral Duration: ongoing

Evidence	Effect	Remarks
	Maintenance treatment with prednisone was started in 1 pt after multiple tapered steroid doses. At 2,5 mg every other day she had an exacerbation, so the dose was increased to 5 mg every other day. She is stable (side effects are not mentioned).	Proposal: -
Ref. 3f Pilot study, n=7 (C)	**Methylprednisolone bolus: a novel therapy for severe atopic dermatitis** (Galli et al. 1994) Summary: 5 pt showed improvement in skin lesions an a dramatic decrease in itching. Symptom relapse persisted from 3 to 18 months (mean 10 months). 2 pt only had a mild improvement in the days after treatment, without a relevant change in itch. No side effects other than transient immunosuppression.	Indication: severe AD Age: 3-14 y (mean 9 y, 7 mo) CS: methylprednisolone Dosage: 20 mg/kg/day Administration: iv Duration: 3 d Proposal: -
Ref. 3g Double-blind, randomized, cross-over trial, n=20 (B)	**A randomized, double-blind, placebo-controlled, crossover trial of systemic flunisolide in the treatment of children with severe atopic dermatitis.** (La Rosa M 1995) Summary: 10 pt started with 2 wks flunisolide, followed by 1 week wash-out and 2 weeks placebo. The other 10 pt started with 2 wks placebo. The non-validated composed endpoint for clinical effect was significantly better after flunisolide treatment. The pruritus score also improved, but less than the other outcomes. After discontinuation of flunisolide there was a small relapse. Both groups had comparable disease severity at the end of the study. No severe adverse effects were reported. NB. The effective daily systemic availability was calculated to be about 128 µg in children younger than 3 years of age and 220 µg in older children. Flunisolide is comparable to triamcinolone in inhalation products (Daley-Yates/Ernst 2006).	Indication: chronic, severe AD Age: 2.4 – 6.2 y (mean 3.6 y) CS: flunisolide Dosage: < 3 y: 640 µg, > 3 y: 1200 µg in 2 doses Administration: oral Duration: 5 wks Proposal: -

Discussion:

Age limit

Treatment of children as young as 6 months has been described for AD. Current recommendations in the KF for indications such as juvenile dermatomyositis and inflammatory bowel disease have a lower age limit of 1 month. In the studies it is described that children can already develop AD within weeks after birth. Treatment with OCS is a last resort, so very young babies are usually not treated with OCS for this indication. To be consistent with immunosuppressant therapies, a lower age limit of 1 or 2 years old is also a possibility.

PROPOSAL: use a lower age limit of 6 months to reflect the use of OCS in daily practice and be in line with literature.

MEETING 10-9-2020: approved.

Treatment duration

In one (old) study children were treated for 1 to 5 months with cortisone. (Solomons 1954) Side effects are not mentioned, but with the newer literature about long term adrenal suppression even after determination of treatment, this would be too long. Three newer studies mention treatment durations of 4 to 5 weeks, although in 1 study dose was tapered to maintenance dose after 4 weeks. The duration of the maintenance dose has not been described. (Heddle et al. 1984, Aylett, Atherton, and Preece 1992, La Rosa M 1995). The Dutch guideline CE mentions OCS can be used for 2-3 weeks during exacerbations or as bridging therapy to immunosuppressant therapy. (NVDV 2019)

QUESTION: in the Dutch guideline Psoriasis OCS are mentioned very briefly, but the use is comparable to AD: only in exacerbations with the lowest possible dose and as short as possible. (NVDV 2017) Should the indication be extended to Exacerbation of atopic dermatitis or psoriasis?
PROPOSAL: alter the indication to: Exacerbatie van atopische dermatitis. Add a remark: Prednisolon kan tevens kortdurend gebruikt worden tijdens het starten van de behandeling met een traagwerkend immunomodulerend middel, zoals azathioprine, mycofenolzuur en methotrexaat.
MEETING 10-9-2020: No board member is familiar with prednisolone use in psoriasis. Indication should not be added.

Dose
Since the treatment duration is short, a difference between initial dose and maintenance dose is not necessary. Dose tapering is recommended, especially in longer treatment durations. Dose tapering reduced the risk of adrenal suppression, but does not prevent a relapse. (NVDV 2019)
In the literature, there is only 1 case report with prednisone. (Sonenthal, Grammer, and Patterson 1993). The used dose in a 7 year old girl was 5 mg every other day, for an unspecified duration. The authors describe the regimen every other day reduces some of the side effects, but does not prevent long term effects like posterior subcapsular cataract formation, the potential for growth retardation and possibly osteoporosis. Other studies used beclomethasone inhalation capsules (Heddle et al. 1984, Aylett, Atherton, and Preece 1992), cortisone (Glaser 1952, Solomons 1954), methylprednisolone bolus (Galli et al. 1994) or flunisolide. (La Rosa M 1995). The used dosages are converted to prednisolone equivalents in the table below.

OCS	**Study 1**	**Study 2**
Beclomethasone	3-14 y: 800 µg = 1,6 mg pred	Age unknown Initial dose: 1800 µg = 3,6 mg pred 1000 µg = 2 mg pred
Flunisolide	< 3 y 128 µg = 0,1 mg pred > 3 y 220 µg = 0,2 mg pred	-
Cortisone	14 y old: 118 mg = 24 mg pred	All 0,5y – 3 y olds: Initial 50-75 mg = 10-15 mg pred 25-50 mg – 5-10 mg pred
Methylprednisolone	3-14 y: 20 mg/kg = 25 mg/kg pred	-

Prednisolone is usually dosed per kg body weight. In other indications in KF this differs from 0,5 mg/kg to 2 mg/kg. The guideline CE mentions a dose of 0.5 mg/kg/day for adults. (NVDV 2019) This would be comparable to the used doses of cortisone. An average 14 year old weighs around 50 kg (0,5 mg/kg = 25 mg prednisolone) and 0,5 – 3 year old weigh between 7 and 15 kg (1 mg/kg = 7 – 15 mg prednisolone). The 7 year old girl using 5 mg prednisolone every other day is relatively low (average weight 24 kg), but this was meant as a chronic dose. The methylprednisolone dose is high if converted to prednisolone, but is normal for methylprednisolone in other indications (such as juvenile dermatomyositis in KF). This therapy is only used for 3 days instead of several weeks. The American guideline mentions a usual dose of 0,5-1 mg/kg/day. (Sidbury et al. 2014)

The doses of beclomethasone and flunisolide are (very) low. These were probably selected to determine if side effects were less with these low doses. In 1 study with beclomethasone there is still growth retardation in 7 out of 10 children. (Aylett, Atherton, and Preece 1992). The initial dose in this study is close to a low therapeutic dose though.
PROPOSAL: 0,5 -1 mg/kg/dag in 1 dosis gedurende 2-3 weken. Als een langere behandeling na zorgvuldige afweging toch nodig is, kan een dosis om de dag overwogen worden. Het afbouwen van de dosering wordt aanbevolen om bijnierschorssuppressie te verminderen.

MEETING 10-9-2020: Prednisolone is used as a short course or as bridging awaiting the effect of an immune-modulator. However, bridging for 2-3 weeks does not cover the period until the immune modulator is showing effect. According to the board, a period of at least 2-3 months is needed.

Choice of OCS
Prednis(ol)on is a common OCS for oral administration in the Netherlands. Methylprednisolone has only been evaluated in 1 study and should be administered iv or im. Cortisone was one of the first available OCS (since 1950), but has both glucocorticosteroid and mineralocorticosteroid effects. Prednisolone (since 1955) has mainly glucocorticosteroid effects, which is beneficial to reduce inflammation.
PROPOSAL: add the indication Atopic dermatitis only to the monography of prednisolone.
MEETING 10-9-2020: approved.

Monitoring
For OCS there is no standard monitoring protocol for laboratory values. The main concern is about side effects such as infections, hyperglycaemia, behavioural change, adrenal suppression, weight gain, growth retardation and cushingoid features. (Aljebab, Choonara, and Conroy 2017). The American and Dutch guideline have the same recommendation for monitoring of side effects: growth-velocity measurement in children and blood pressure monitoring, ophthalmologic examination, hypothalamic-pituitary-adrenal axis suppression testing and bone density evaluation in adults. If there is pre-existing diabetes, blood glucose measurements are also recommended. (NVDV 2019)
The most common side effects are infections, just as in other immunosuppressant drugs. Information should be provided to the patient and carers about the possibility of infections. Weight gain and cushingoid features are also side effects that can also be examined at scheduled doctors' visits. Both side effects are common (weight gain: 21.1%; cushingoid features: 19.4%). Cushingoid features were also a reason for 4 children to discontinue treatment. (Aljebab, Choonara, and Conroy 2017)

<u>Growth retardation</u>
One case described the improvement of growth by using an OCS: a 10 month old infant with severe AD, hypoalbuminemia, anemia and edema (related to the AD) did not grow since the infant was 5 months old. Treatment with 2 mg/kg prednisone for 1 month was effective for the atopic dermatitis and the hypoalbuminemia, anemia and reduced growth. After discontinuation of prednisone, the AD worsened and he was treated with topical creams and ointments. Side effects are not described. (Abrahamov et al. 1986)
In most children it is of course the other way around: growth retardation was found in 18.1% of children with long term treatment. It was not described in short term treatment (≤ 15 days). (Aljebab, Choonara, and Conroy 2017).
Maybe the age of the child is also relevant: in the Informatorium Medicamentorum it is mentioned the effect on the final length of the child is probably not affected if OCS are terminated before the growth spurt in puberty. (KNMP 2020b) A dose every other day could also reduce the growth retardation.
For inhalation corticosteroids, there are recommendations to check this every 3 months. Since these doses are considerably lower and the treatment with OCS should not exceed a couple of weeks, this recommendation is not applicable for atopic dermatitis. A practical recommendation would be to check the growth every month during therapy. Growth measurement after termination of therapy is not necessary: the OCS are already terminated, so noted growth retardation will not lead to treatment alteration.
PROPOSAL: monitor growth during therapy with OCS every month.
MEETING 10-9-2020: Every month is too quick; it's enough to do this every 3 months

<u>Adrenal suppression</u>
One (recent!) case describes a classic adrenal suppression: a 12 y old boy was treated with an over-the-counter oral solution containing 15 mg prednisolone/5 mL. He used a 'spoonful' two to three times a week for the past 6 years. (NOTE: a teaspoon is 3 mL, a dining spoon 15 mL, corresponding to 9 mg resp. 45 mg prednisolone every other day). He presented with a moon face, a BMI of 98.52 kg/m^2, a fat pad in his neck and pubic hair. Insulin was 30.4 µIU/mL (normal 2.6-24.9), ASAT 49 IU/L (normal 0-40) and ALAT 90 IU/L

(normal 0-30 IU/L). This indicates insulin resistance and hepatotoxicity due to exogenous corticosteroid use. He started hydrocortisone 10 mg/m^2/d with a slow taper of 2-3 months. Follow-up is not described. The authors discuss a 4 week course with OCS suppresses the HPA-axis for 8 weeks after treatment determination (in children with leukemia). Prolonged therapy, as seen in this case, can result in adrenal suppression for up to 9 months. (O'Brien, DeKlotz, and Silverman 2018)

Adrenal suppression is very common. 58.6% of children experienced HPA-axis suppression, both in short-course and long-course therapy. (Aljebab, Choonara, and Conroy 2017). The HPA-axis suppression is restored after termination of treatment. The length of suppression is related to the duration of the OCS therapy. After long course treatment it will take months before the function has normalized. The suppression will be less if the OCS dose is gradually tapered.
QUESTION: when is an ACTH test indicated (if indicated at all)? And what should be the recommendation if the HPA-axes suppression persists and leads to serious complaints?
PROPOSAL: An ACTH test is not indicated, since the cause of the suppression is known. If the suppression persists with serious complaints after treatment termination a low dose OCS can be restarted an tapered slower than before.
MEETING 10-9-2020: advise to contact a paediatric endocrinologist in case of suspicion of adrenal suppression.

Hypertension and diabetes
The current KNMP recommendations for OCS in patients with *pre-existing* hypertension and diabetes are:
Hypertension: if > 7,5 mg prednisolone/day: check blood pressure (every month)
Diabetes: if > 7,5 mg prednisolone/day: regularly check blood glucose (KNMP 2020a)
This signal will also pop-up in children with these indications. For other children, the systematic review mentions 5.6% of children developed hypertension and 3.4% hyperglycaemia. (Aljebab, Choonara, and Conroy 2017). Although the incidence is relatively low, both side effects were reasons to cease treatment. Some children needed antihypertensive treatment or insulin, but in most cases the effect was transient and resolved shortly after OCS termination. On the other hand, 2 children died because of hyperglycaemia.
QUESTION: is a blood pressure measurement and/or glucose measurement before, during and after treatment indicated? 7.5 mg prednisolone could be used as cut off value.
PROPOSAL: measure blood pressure. If there is increased blood pressure at two consecutive measurements, taper dose or discontinue treatment. For hyperglycaemia, information about symptoms is provided. Standard glucose testing is not indicated.
MEETING 10-9-2020: approved.

Osteoporosis
When OCS are used in high doses, osteoporosis prophylaxis is indicated (in adults). The clinical rule on the KNMP Kennisbank includes children, although the prednisolone dose should be > 15 mg/day to trigger an automated pop-up during prescribing. Decreased bone density is often detected in paediatric studies (21,1% of studies), but osteoporosis is rarely detected (0,8%). Routine monitoring for osteoporosis seems unnecessary.
PROPOSAL: If a fracture occurs during or shortly after OCS treatment bone density measurement is indicated.
MEETING 10-9-2020: approved.

Depression
Depression is a known contra-indication for OCS. One case report mentions the treatment with OCS even helped to treat the depression. (Glaser 1952). The KNMP Kennisbank mentions very high doses (≥ 40 mg prednisolone per day) can cause depressive symptoms or worsen existing depression. (KNMP 2020a) In the systematic review in children behavioural changes were twice as common in long term treatment (> 15 days) than short term treatment (8.1% resp. 4.7%). (Aljebab, Choonara, and Conroy 2017). In 9 children

behavioural change was the reason to cease treatment. Besides depression also insomnia, mood change and dementia have been reported.
QUESTION: is behavioural change something to discuss? Or is the therapy too short?
MEETING 10-9-2020: Yes, include in side effects

Glaucoma
Glaucoma is not reported in the systematic review for OCS side effects in children. (Aljebab, Choonara, and Conroy 2017). If there is no pre-existing glaucoma, monitoring is not necessary.

Vaccinations
Booster immunization may be needed in long-term OCS use. (Sidbury et al. 2014) This is not applicable in short-term use. Vaccines in general should be discussed, since vaccination with an alive pathogen is also problematic during immunosuppressant use.
PROPOSAL: provide information about vaccination.
MEETING 10-9-2020: approved.

Pregnancy
Prednisolone (or other OCS) can be used during pregnancy. Information about this subject is not necessary, since the growth retardation on the foetus is mainly during long-term, high-dosed therapy.
PROPOSAL: specific attention for pregnancy is not needed.
MEETING 10-9-2020: approved.

Handbook 1 BNF for children 2018-2019	Indication not mentioned	Remarks:
Handbook 2 Pediatric & neonatal dosage handbook 25th edition	Indication not mentioned	Remarks:
Handbook 3 IBM Micromedex®	Indication not mentioned (several OCS)	Remarks:
Handbook 4 Drug prescribing in renal failure, 5th edition 2007	GFR 30-50: 100% GFR 10-29: 100% GFR <10: 100% IHD: 100% PD: 100% CRRT: 100% (D)	Standard dosage: Consult paediatric reference; doses vary upon indication

General discussion:
M. van den Berg indicated that with long term use, calcium and vitamin D should be suppleted. (Dogru 2018, Sánchez-Armendáriz et al. 2018) support this. Therefore this is added in warnings and precautions in children.

Additional information:
Renal function:
- Current KF: Aanpassing van de dosering is niet nodig.
- KNMP: -
- SmPC: -
- Pubmed: no information
- Proposal: maintain the current information in KF.

Pharmacogenetics KNMP: no information

Obesity: Dose on total body weight (TBW). As TBW increases, clearance of prednisone increases linearly. To maintain adequate serum concentrations, dosing based on TBW is required. (Ross et al. 2015)

Proposal meeting (10/09/2020):

Section	Proposal	Results meeting
Dosering - Indicatie	Exacerbatie van atopische dermatitis of psoriasis	Psoriasis should not be added
Dosering	Age limits: 6 mo -18 y	Approved
Dosering	0,5-1 mg/kg/dag in 1 dosis gedurende 2-3 weken	Dosage approved, duration of 2-3 weeks is removed. A max of 60 mg is added in case of a prednisolone course and a max of 40 mg/day in case of bridging until the immune modulator, like AZA, CsA of MMF, shows efficacy.
Dosering	Prednisolon kan tevens kortdurend gebruikt worden tijdens het starten van de behandeling met een traagwerkend immunomodulerend middel, zoals azathioprine, mycofenolzuur en methotrexaat	Not approved, remove information
Dosering	Als een langere behandeling na zorgvuldige afweging toch nodig is, kan een dosis om de dag overwogen worden. Het afbouwen van dosering wordt aanbevolen om bijnierschorssuppressie te verminderen.	Approved, specify tapering with duration of therapy after which tapering should take place (after >10 days)
Waarschuwingen en voorzorgen bij kinderen	Bij overgewicht kunnen doseringen aan de hoge kant van het doseringsbereik nodig zijn voor een goede respons, nauwgezette monitoring wordt aanbevolen.	Approved
Waarschuwingen en voorzorgen bij kinderen	Add monitoring information:	
Waarschuwingen en voorzorgen bij kinderen	Bespreek de grotere kans op huidinfecties en de symptomen van een hyperglykemie.	Approved
Waarschuwingen en voorzorgen bij kinderen	Controleer eventuele gewichtstoename en cushing-achtige symptomen (vollemaansgezicht).	Approved
Waarschuwingen en voorzorgen bij kinderen	Controleer elke maand de lengte om eventuele groeiremming vast te stellen.	Not every month but every 3 months
Waarschuwingen en voorzorgen bij kinderen	Controleer de bloeddruk. Indien deze bij 2 opeenvolgende controles verhoogd is, bouw prednisolon (langzaam) af.	Approved
Waarschuwingen en voorzorgen bij kinderen	Besteed aandacht aan vaccinatie adviezen tijdens prednisolon gebruik.	Approved
Waarschuwingen en voorzorgen bij kinderen	Een ACTH test kan overwogen worden als na staken nog steeds invaliderende klachten van bijnierschorssuppressie aanwezig zijn. Mogelijk is te snel afgebouwd en is een lage dosering prednisolon met een meer geleidelijke afbouw nodig.	Approved, add recommendation to contact a paediatric endocrinologist in case of suspicion of adrenal suppression
Waarschuwingen en voorzorgen bij kinderen	Het meten van de botdichtheid kan overwogen worden bij een fractuur tijdens of vlak na de behandeling met prednisolon.	Approved
Bijwerkingen bij kinderen	Add: Hypertensie, depressie.	Approved
Bijwerkingen bij kinderen	Add: Cushing-achtige verschijnselen Replace: vetzucht door gewichtstoename Bij langdurig gebruik van suprafysiologische doseringen: groeiremming en osteoporose, naast maagdarmulcera, verminderde afweer tegen infecties, vetzucht en onderdrukking van de hypothalamus-hypofyse bijnieras.	Approved. Also add behavioural changes, like dysphoric behaviour, hyperactivity and insomnia

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