**National Essential Medicine List**

**Paediatric Medication Review Process**

**Component: The Nervous System**

**MEDICINE MOTIVATION:**

1. **Executive Summary**

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| **Date:**  July 2019  **Medicine (INN):** Prednisone  **Medicine (ATC):** H02AB07  **Indication (ICD10 code):** Duchenne Muscular Dystrophy (G71.0)  **Patient population:** Children  **Prevalence of condition:**  1 in 5000 live male births[[1]](#endnote-1)  **Level of Care:** Specialist consultation  **Prescriber Level:** Tertiary consultation, Secondary initiation/management  **Current standard of Care:** Prednisone  **Efficacy estimates: unable to calculate NNT**  **Primary outcome:**  Average muscle strength: Prednisone vs placebo (baseline to 12 weeks) LS mean 0.37 vs -0.1 p = 0.0002, 95% CI 0.15–0.59  **Secondary outcome:**  Nine-metre walk/running time after 6 months on treatment: Prednisone 0.75 mg/kg/day vs placebo mean difference -2.37 (-3,97 to -1.50)  Four-stair climbing time after 6 months on treatment: Prednisone 0.75 mg/kg/day vs placebo mean difference -3.09 (-4.33 to -1.85) |

1. **Name of author(s)/motivator(s):** Paediatric Expert Review Committee
2. **Author affiliation and conflict of interest details** No specific conflicts identified.
3. **Introduction/ Background**

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder causing progressive muscle weakness, typically in males. Affected patients typically become wheelchair-bound prior to adolescence. DMD results from a mutation in the gene coding for dystrophin.[[2]](#endnote-2) The management of DMD with glucocorticoid therapy has long since been established. However, the condition has not previously been included in the Paediatric Hospital Standard Treatment Guidelines and Essential Medicines List and thus we provide the evidence base for the medicine treatment. The decision to include this condition was prompted by a suggestion received when the 2017 version of the CNS chapter was distributed for comment. It was noted that the ongoing management of DMD is frequently stepped down to the secondary level hospitals once patients are diagnosed and established on treatment. As such a summary on DMD and its management was deemed a valuable inclusion for hospital level practioners. The recommendation is to commence treatment with glucocorticoids therefore designated as ‘in consultation with a specialist’. This as the timing of initiation of glucocorticoids in patients with DMD can be tricky and requires experience.

The purpose of this motivation is to detail the glucocorticoid regimen that provides the maximal benefit to patients with DMD while keeping adverse effects to a minimum.

1. **Purpose/Objective i.e. PICO:**

**-P** *(patient/population):* Children with DMD

**-I** *(intervention):* Prednisone

**-C** *(comparator):* Placebo OR Prednisone 1.5 mg/kg/day OR Prednisone with varying dosing schedules

**-O** *(outcome):* Maintenance of motor function, delay in loss of ambulation, time taken to rise from the floor, mean change in average muscle score, nine-metre walking/running time, 4 stair climbing time.

1. **Methods:**
   1. **Data sources:** Pubmed, Cochrane Library
   2. **Search strategy**

Search 1: Pubmed

("muscular dystrophy, duchenne"[MeSH Major Topic] AND ("prednisone"[MeSH Terms] OR "prednisone"[All Fields])) AND randomized controlled trial[Publication Type]

11 results yielded,

10 studies excluded

Search 2: Cochrane Library

 "Duchenne muscular dystrophy" in Title Abstract Keyword AND "prednisone" in Keyword AND "randomised control trial" in Publication Type - (Word variations have been searched)

19 results yielded, no additional studies for inclusion.

Search 3: Cochrane Library

“Prednisone’ or “corticosteroid” and “duchenne muscular dystrophy”

Identifed an additional study – Matthews et.al.

* 1. **Excluded studies:**

|  |  |  |
| --- | --- | --- |
| ***Author, date*** | ***Type of study*** | ***Reason for exclusion*** |
| *Guglieri, et al 2017* | *Study protocol* | *Ongoing study* |
| *Kirschner, et al 2010* | *RCT* | *Ciclosporin vs placebo* |
| *Tarnopolsky, et al 2004* | *RCT* | *Crossover trial with creatinine monophosphate and placebo* |
| *Shieh, et al 2018* | *Post-hoc analysis* | *Pred vs deflazacort, not placebo controlled* |
| *Bello 2015* | *Observational* | *Not RCT* |
| *Bonifati 2000* | *RCT* | *Included in Cochrane Review* |
| *Hu, et al 2015* | *RCT* | *Included in Cochrane Review* |
| *Beenakker, et al 2005* | *RCT* | *Included in Cochrane Review* |
| *Escolar, et al 2011* | *RCT* | *Included in Cochrane Review* |
| *Connolly, et al 2002* | *Case control study* | *Not RCT* |
| *Buyse, et al 2014* | *RCT* | *Idebenone vs glucocorticoids* |
| *Mendell, et al 2013* | *RCT* | *Eteplirsen vs placebo* |
| *Fenichel, et al 1991* | *RCT* | *? included in CR* |
| *Kissel, et al 1993* |  | *Not relevant to PICO question* |
| *Kissel, et al 1991* |  | *Not relevant to PICO question* |
| *Escolar, et al 2005* | *RCT* | *Trial of creatine and glutamine, not relevant to PICO question* |
| *Burrow, et al 1991* |  | *Not relevant to PICO question* |

* 1. **Evidence synthesis**

Meta-analysis

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| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Author, date*** | ***Type of study*** | **n** | **Population** | **Comparators** | **Primary outcome** | **Effect sizes** | **Comments** |
| Matthews et.al 20163 | Cochrane review and meta-analysis | 12 studies (667 participants) | Patients with DMD | Corticosteroid vs placebo, weekend only vs daily prednisone, deflazacort vs prednisone | Primary:  Prolongation of time to loss of ambulation  Secondary:   * Strength outcome measure * Functional outcome measures * Pulmonary function * Quality of life * Adverse events | Primary outcome: Deflazacort – data not adequate to draw conclusions  Secondary:   * Prednisone 0.75mg/kg/day shown to improve muscle strength and function versus placebo over 6 months | Moderate quality evidence |

Randomised controlled trials (RCT)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Author, date*** | ***Type of study*** | **n** | **Population** | **Comparators** | **Primary outcome** | **Effect sizes** | **Comments** |
| Griggs 20164 | RCT | 196 | Boys aged 5-15 years with DMD | Placebo, deflazacort 0.9 mg/kg/d, deflazacort 1.2 mg/kg/d, prednisone 0.75 mg/kg/d | * Primary:   Average muscle strength by modified MRC scale at 12 weeks   * Secondary:   Average muscle strength from week 12 to week 52;  Timed functional testing: time from supine to standing, time to climb 4 stairs, time to run or walk 30 feet | Change in average muscle strength score: Pred vs Placebo (baseline to 12 weeks) Least Squares (LS) mean 0.37 vs -0.1 p = 0.0002, 95% CI 0.15–0.59   * Secondary: \*   Time from supine to standing:  Pred vs placebo  Time to rise from supine to standing p = 0.0016  Time to climb 4 stairs p = 0.0001  Time to run/walk 30 feet p = 0.0001  \*actual effect size not captured in study | Intention to treat population used.  Biphasic trial, groups well randomized, multiple drugs/doses vs placebo arm in phase 1. Phase 2 of trial excluded the placebo arm, randomising all patients to one of the active treatment arms.  More adverse effects in the prednisone treatment group (vs Deflazacort) with weight gain being most common. |

* 1. **Evidence quality:**

One meta-analysis and one additional RCT show objective improvement in average muscle strength and improved performance on timed functional tests once corticosteroid therapy is commenced. These data were collected for males affected with DMD prior to loss of ambulation. Multiple corticosteroids were trialed at various doses, showing deflazacort 0.9 mg/kg/d and prednisone 0.75 mg/kg/d as the most efficacious for various outcomes. The adverse effect profile associated with long term use of corticosteroids remains of concern. The most commonly used treatments are prednisone and deflazacort. The evidence for the use of prednisone 0.75 mg/kg daily shows more benefit in terms of primary end points used as well as an adverse effect profile superior to those experienced by patients on higher doses of the prednisone. Alternative dosing schedules have been proposed and trialed (e.g. daily dosing for 20 days followed by 10 drug free days or higher dose prednisone biweekly or daily dosing on weekdays with drug free weekend).

1. **Alternative agents:**

* Deflazacort 0.9 mg/kg/day (improved adverse effect profile as compared to prednisone, Griggs 2016): Medication not currently available in SA. This condition should be flagged for review when Deflazacort is registered for use in South Africa.
* Idebenone has been shown to be safe and well tolerated in a phase IIa double-blind randomized controlled clinical trial.5

**EVIDENCE TO DECISION FRAMEWORK**

|  | **JUDGEMENT** | **SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS** |
| --- | --- | --- |
| **QUALITY OF EVIDENCE** | **What is the overall confidence in the evidence of effectiveness?**   |  |  |  | | --- | --- | --- | | Confident | Not confident | Uncertain | | |  | | --- | | X | | |  | | --- | |  | | |  | | --- | |  | | | Standard of care |
| **BENEFITS & HARMS** | **Do the desirable effects outweigh the undesirable effects?**   |  |  |  | | --- | --- | --- | | Benefits outweigh harms | Harms outweigh benefits | Benefits = harms or Uncertain | | |  | | --- | | X | | |  | | --- | |  | | |  | | --- | |  | | |  |
| **THERAPEUTIC INTERCHANGE** | Therapeutic alternatives available:   |  |  | | --- | --- | | Yes | No | | |  | | --- | |  | | |  | | --- | | X | |   List the members of the group.  List specific exclusion from the group: | Rationale for therapeutic alternatives included:  References:  Rationale for exclusion from the group:  References: |
| **VALUES & PREFERENCES /**  **ACCEPTABILITY** | **Is there important uncertainty or variability about how much people value the options?**   |  |  |  | | --- | --- | --- | | Minor | Major | Uncertain | | |  | | --- | |  | | |  | | --- | |  | | |  | | --- | | X | |   **Is the option acceptable to key stakeholders?**   |  |  |  | | --- | --- | --- | | Yes | No | Uncertain | | |  | | --- | | X | | |  | | --- | |  | | |  | | --- | |  | | |  |
| **RESOURCE USE** | **How large are the resource requirements?**   |  |  |  | | --- | --- | --- | | More intensive | Less intensive | Uncertain | | |  | | --- | |  | | |  | | --- | | X | | |  | | --- | |  | | | Cost of medicines/ month:   |  |  | | --- | --- | | **Medicine** | **Cost (ZAR)/month\*** | | Prednisone 0.75mg/kg/day | R21.52  (30kg child) |   *\*Master procurement catalogue – September 2019*  **Additional resources:** |
| **EQUITY** | **Would there be an impact on health inequity?**   |  |  |  |  | | --- | --- | --- | --- | | Yes |  | No | Uncertain | | |  | | --- | |  | |  | |  | | --- | |  | | |  | | --- | | X | | |  |
| **FEASIBILITY** | **Is the implementation of this recommendation feasible?**   |  |  |  | | --- | --- | --- | | Yes | No | Uncertain | | |  | | --- | | X | | |  | | --- | |  | | |  | | --- | |  | | |  |

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| [**Type of recommendation**](#TypeofRecommendation_C) | We recommend against the option and  for the alternative | We suggest not to use the option or  to use the alternative | We suggest using either the option or the alternative | We suggest  using the option | We recommend  the option |
|  | |  | | --- | |  | | |  | | --- | |  | | |  | | --- | |  | | |  | | --- | |  | | |  | | --- | | **X** | |
| [**Recommendation**](#TypeofRecommendation_C)  **Rationale:**  **Level of Evidence:**  **Review indicator:**   |  |  |  |  | | --- | --- | --- | --- | | Evidence of efficacy |  | Evidence of harm | Price reduction | | |  | | --- | |  | |  | |  | | --- | | X | | |  | | --- | |  | |   **VEN status:**   |  |  |  | | --- | --- | --- | | Vital | Essential | Necessary | | |  | | --- | | X | | |  | | --- | |  | | |  | | --- | |  | | | It is recommended that prednisone 0.75 mg/kg/day be included for the specialist initiation in DMD.  Standard of care  LoE II | | | | |
| **[Monitoring and evaluation](#Monitoring" \o "What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option?) considerations** | Long term use of corticosteroids is associated with various complications. Monitor patients and manage as needed. | | | | |

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Excluded studies:

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1. [↑](#endnote-ref-1)
2. [↑](#endnote-ref-2)