Long-term follow-up of safety and disease control for hydrocortisone granules designed to give age-appropriate dosing with taste masking to children with adrenal insufficiency

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Context: Alkindi® (Hydrocortisone granules in capsules for opening), was developed by Diurnal Ltd., a pharmaceutical company developing endocrine products, and was recently licensed for oral administration to children with adrenal insufficiency (AI) from birth to 18 years. Previously, children received pharmacy compounded capsules to achieve age appropriate dosing, however almost 25% of batches were out of specification for mass and content uniformity and clinically evident under- and over-dosing was reported.

Conclusions: Alkindi® is a newly developed paediatric and neonatal formulation of immediate release hydrocortisone that is provided in appropriate unit dosage (0.5, 1 mg, 2 mg and 5 mg). Alkindi® was well tolerated with neither adrenal crisis nor AEs reported related to Alkindi® treatment. The most frequently reported AEs were infections, which were managed appropriately using sick day rules. There was no indication of either under-treatment or over-treatment, which is important for achievement of disease control in the growing child.

Patients and study design:
Open label, long term follow up, single centre study.

24 children completed the Alkindi® Phase 3 trial

18 children enrolled in this extension study

12 children finished this extension study. Last patient last visit – 10th Aug 2018

6 children or parents not willing for a further study

6 children withdrew early by „withdrawal of consent” mainly due to problems with taking the late night dose during the sleep

Demographics:

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/4</td>
<td>4/2</td>
</tr>
<tr>
<td>diagnoses</td>
<td>9 - CAH</td>
<td>5 – CAH</td>
</tr>
<tr>
<td>Median ages at entry</td>
<td>1316 days (~3 years, 7 months)</td>
<td>747 days (~2 years)</td>
</tr>
<tr>
<td>Mean duration of treatment (until 22nd Mar 2018)</td>
<td>326 days (~1 year)</td>
<td>635 days (~1.7 years)</td>
</tr>
<tr>
<td>Finishing study and continuing therapy after commercial supply</td>
<td>n=4</td>
<td>n=5</td>
</tr>
</tbody>
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Conclusions: Overall mean daily dose ranged from 6.01 to 8.51 mg (10.4-12.0 mg/m² BSA) administered according to usual clinical practice (3x/day). No changes in vital signs occurred that indicated an adverse effect of Alkindi®, no trends for accelerated or reduced growth (Z-scores).

Adverse events:
A total of 170 treatment-emergent adverse events (TEAEs) were recorded in 14 subjects (77.8%) overall.

Severe adverse events:
Eight SAEs occurred in 3 patients, not related to Alkindi®. No cases of adrenal crisis, no AEs of choking.

References: Neumann, Whitaker et al., Clinical Endocrinology 2018;88:21–29
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