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Date 10 December 2019
Subject Letter report GVS assessment hydrocortisone granulate in capsules to be opened 0.5, 1, 2 or 5 mg (Alkindi®)

Dear Mr Bruins,

In your letter of 16 April 2019 (CIBG-19-08029), you asked National Health Care Institute to assess the medicinal product Alkindi®.

The marketing authorisation holder for Alkindi® has submitted an application for the inclusion of this medicinal product on List 1B of the Health Insurance Regulation. The National Health Care Institute will answer your question on the basis of a limited review.

Alkindi® contains hydrocortisone. It is indicated for substitution therapy for adrenal insufficiency in infants, children and adolescents (from birth to < 18 years). Each capsule contains 0.5, 1, 2 or 5 mg hydrocortisone.
The dosage must be adjusted to the response of the individual patient. The lowest possible dosage should be used.
Recommended replacement doses of hydrocortisone are 8-10 mg/m^2/day for patients with adrenal insufficiency only, and 10-15 mg/m^2/day for patients with congenital adrenal hyperplasia (CAH), typically divided into three or four doses.
In situations where the body is exposed to excessive physical and/or mental stress, patients may need to be given an increased dose, especially in the afternoon or evening.

Introduction
To determine the place of a medicinal product in the Medicine Reimbursement System (GVS), its interchangeability with medicinal products already included in the GVS must first be assessed.

Cluster 0H02ABC0 V includes medicinal products with a similar indication area, i.e. hydrocortisone 20 mg tablet (Tiofarma), Plenadren® 5 mg and 20 mg tablet (with hydrocortisone mga), and cortisone 5 mg and 25 mg tablet (Teva). However, the available hydrocortisone or cortisone trade preparations are intended for use by adults. The available strengths of these trade preparations do not match the dosages for children. This is confirmed in the paediatric formulary. Children are therefore currently prescribed pharmacy preparations with hydrocortisone in lower strengths. Alkindi® (hydrocortisone) is the only trade preparation recently

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registered for "substitution therapy for adrenal insufficiency in infants, children and adolescents (from birth to < 18)".

The medicinal products from cluster 0H02ABC0 V are available as trade preparations in the range of 5 mg - 25 mg. These strengths do not match the paediatric doses. The pharmacy preparations currently used for children are available from 1 mg per capsule, tablet or ml drink. According to the paediatric formulary, hydrocortisone is dosed as 8-12 mg/m^2/day in 3 doses (ratio 2:1:1). For example, a 4-year-old child with a dose of 10 mg/m^2/day and a body surface of 0.7m^2 should receive 7 mg hydrocortisone per day in 3 doses (ratio 2:1:1). This example shows that the existing trade preparations do not provide a solution for children.
The pharmacy preparations that are now used for children have been developed in collaboration with representatives of patients and practitioners. These products are available in paediatric-appropriate forms of administration, using tablets in different colours.

Alkindi® contains granulate in capsules for opening, and is specifically designed for use by children. The capsule shell should not be swallowed, but opened in a specific way. The granules must be administered orally without chewing. After administration, the child should be made to drink immediately, for instance water, milk, breast milk or bottle feeding, to ensure that all granules are swallowed. If the granulate is sprinkled on a spoon with soft food, it should be administered immediately (within five minutes) and not stored for later use. The granulate cannot be added to liquid as the whole dose might not be ingested this way, and the bitter taste of hydrocortisone may not be masked properly.

Assessment of interchangeability
Alkindi® is not interchangeable with the other medicinal products in the GVS on the basis of the criteria currently in force. There is a difference in age category compared to the hydrocortisone preparations included in cluster 0H02ABC0V. Alkindi® has a form of administration specifically developed for children. Based on the above, Alkindi® cannot be placed on List 1A. It should be reviewed whether Alkindi® is eligible for inclusion on List 1B.

Therapeutic value
Adrenal insufficiency is a condition in which the adrenal glands produce no or insufficient amounts of corticosteroid hormones. The treatment consists of substitution of deficiencies, crisis management and education/coaching. The shortage of cortisol is usually substituted with hydrocortisone, which is most similar to the natural cortisol. The desirable and undesirable effects of hydrocortisone depend on the correct adjustment of the dosage. The dosage must be adjusted to the response of the individual patient.

Alkindi® is specifically developed for use in children with adrenal insufficiency. The registration is based on a paediatric study plan (*Paediatric Investigational Plan),* where bioequivalence has been demonstrated in relation to the reference medicinal product hydrocortisone tablets 10 mg.

Budget impact analysis
In this budget impact analysis, the number of patients eligible for treatment with Alkindi® is estimated to be at least 315 and up to 386. Alkindi® capsules are

packed in bottles of 50 capsules. The pharmacy purchase price (AIP) per pack of 50 capsules is as follows: Alkindi® 0.5 mg (AIP €41.70), 1 mg (AIP €83.11), 2 mg (AIP €165.83), and 5 mg (AIP €413.99).
For Alkindi®, the price per mg hydrocortisone is €1.66; this is the same for all dose strengths. The cost of the prepared hydrocortisone preparations (in the solid oral forms of administration) is different. It ranges from €0.04 per mg (capsule) to €0.37 per mg (tablet). The average dose of hydrocortisone is estimated at 9 mg/m^2 body surface for adrenal insufficiency and 12.5 mg/m^2 for CAH.

If the substitution of the currently available hydrocortisone preparations (re-delivered) from compounding pharmacies is taken into account, the additional costs are estimated at a maximum of €1.82 to €2.23 million in the third year after admission to the health care package. For this calculation, it was assumed that all patients will switch to Alkindi®.

Consultation
BijnierNet, a foundation for healthcare professionals and patients with adrenal diseases, has indicated that Alkindi® has no clear added value for the Dutch market compared with the available pharmacy preparations, and that it does entail risks. For example, in the pharmacy preparation, children currently have to swallow a small (coloured) tablet. For the proper administration of Alkindi®, the registration text describes detailed instructions that must be followed to avoid medication errors. Children, who may have to take their medication without supervision at school, would have to change their way of taking it, which in theory could result in medication errors. The question is whether (all) children are able to carry out these additional actions correctly without supervision, as indicated in the registration text. BijnierNet expects that a complicated intake will not promote patient compliance.
The professional group (section Paediatric Endocrinology of the Dutch Paediatric Association) also indicated that the use of Alkindi® is a clear risk because this requires more from the children to use the medicinal product correctly.
Finally, health insurers also point out the importance of keeping the pharmacy preparation available.

Advice
Based on the applicable criteria, Alkindi® is not interchangeable with the other oral hydrocortisone preparations included in the GVS as substitution therapy for adrenal inefficiency because it is a form of administration specifically aimed at children. It is therefore eligible for inclusion on List 1B. The additional costs compared to pharmacy preparations are estimated at €1.82 to €2.23 million in the third year after inclusion in the health care package. Inclusion in the GVS fits your policy to prefer registered products in general.

In connection with the care expressed by patients and practitioners about substitution of a (re-delivered) pharmacy preparation by Alkindi®, we would also like to draw your attention to the following. For some of the patients where the prescriber is of the opinion that the substitution of the pharmacy preparation by Alkindi® poses a risk to the correct use, the continued availability of the pharmacy preparation could be beneficial and thus prevent possible medication errors.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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