HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

10 February 2010

ADIXONE 50 µg, tablet
Box of 30 (CIP: 390 604.3)
Box of 60 (CIP: 390 606.6)
Box of 90 (CIP: 390 607.2)
Box of 120 (CIP: 390 608.9)

Applicant: GENOPHARM

Fludrocortisone

ATC code: H02AA02

List I

Date of Marketing Authorization: 4 December 2008 (national)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fludrocortisone

1.2. Background

ADIXONE is the first pharmaceutical product based on fludrocortisone in a dose of 50 µg with a Marketing Authorization in mineralocorticoid replacement therapy for adrenal insufficiency in adults and children in combination with a glucocorticoid. It will replace the hospital preparation, Fludrocortisone AP-HP, available in France since 1972. The Marketing Authorization obtained for this product, unlike the hospital preparation, enables fludrocortisone to be made available in a community setting as well as in hospital.

1.3. Indications

"Mineralocorticoid replacement therapy in the course of primary adrenal insufficiency of any origin, or secondary adrenal insufficiency, in combination with a glucocorticoid".

1.4. Dosage

"Newborn and during the first year of life: 50-200 micrograms per day, and exceptionally 200-300 micrograms per day.

Adults and children over 2 years of age: 50-200 micrograms per day.

The fludrocortisone dosage must be adjusted depending on arterial blood pressure, potassium and sodium serum levels and plasma renin activity which should stay at the upper limit of the normal range.
The dosage must be reevaluated regularly in the course of treatment."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

H	:	Systemic hormonal preparations, excl. sex hormones and insulins
H02	:	Corticosteroids for systemic use
H02A	:	Corticosteroids for systemic use, plain
H02AA	:	Mineralocorticoids
H02AA02	:	Fludrocortisone

2.1.1. Comparator medicines

No other medicinal product based on fludrocortisone exists which is administered orally.

2.2. Medicines with a similar therapeutic aim

There is no medicine with a similar therapeutic aim.

Note:

- Other mineralocorticoid: SYNCORTYL 10 mg/ml (desoxycortone), solution for intramuscular injection , is indicated in "mineralocorticoid replacement for acute adrenal insufficiency"

- Glucocorticoids: medicinal products based on hydrocortisone are indicated in adrenal insufficiency (primary, acute, transitory neonatal, congenital adrenal hyperplasia with or without salt-losing syndrome)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The Marketing Authorization for fludrocortisone (ADIXONE), the use of which as an active ingredient is well established, is based on a bibliographical dossier which includes seven studies published between 1979 and 1996, conducted in a small number of patients (4-23) and which did not have the evaluation of efficacy as an objective.

Presentation of the studies

Four studies[1,2,3,4] were conducted in adults with primary adrenal insufficiency, essentially Addison's disease, who had been receiving glucocorticoid (hydrocortisone 20-40 mg/day or cortisone acetate 37.5-75 mg/day) and mineralocorticoid (fludrocortisone 25-300 µg/day) replacement therapy for several months or years.

The objective of these studies was to:
- evaluate the benefit of measuring atrial natriuretic peptide and renin in the follow-up of mineralocorticoid treatment in Addison's disease
- identify the best biochemical parameters which can be used to detect any mineralocorticoid excess

[1]Cohen N. et al. Atrial Natriuretic Peptide and Plasma Renin Levels in Assessment of Mineralocorticoid Replacement in Addison's disease. J Clin Endocrinol Metab 1996; 81(4): 1411-1415
[2]Thompson Dg et al. Mineralocorticoid replacement in Addison's disease. Clin Endocrinol 1979; 10(5): 499-506
[3]Flynn MD et al. Oedema in patients with Addison's disease on replacement therapy: glucocorticoid excess and mineral corticoid deficiency? Q J Med 1994; 87 (7): 437- 441
[4]Fiad TM et al. The role of plasma rennin activity in evaluating the adequacy of mineralocorticoid replacement in primary adrenal insufficiency. J Clin Endocrinol Metab 1996; 45: 529- 534
[5]Lopes LA et al. Should we monitor more closely the dosage of 9 alpha-fluorohydrocortisone in salt-losing congenital adrenal hyperplasia? J Pediatr Endocrinol Metab 1998; 11(6):733-737
[6]Hughes I A et al. Continuing need for mineralocorticoid therapy in salt-losing congenital adrenal hyperplasia. Arch Dis Child 1979; 54(5):350-355
[7]Hochberg Z et al. Requirement of mineralocorticoid in congenital adrenal hyperplasia due to 11beta- hydroxylase deficiency. J Clin Endocrinol Metab 1986; 63(1):36-40

- verify, in patients with oedema, good adaptation to glucocorticoid and mineralocorticoid treatment by measurement of plasma renin and cortisol
- show the usefulness of measuring plasma renin as an index of adjustment to treatment with fludrocortisone

Three studies[5,6,7] were conducted in children and adolescents (4-15) with congenital adrenal hyperplasia. The objective of these studies was to:
- evaluate the benefit of close monitoring of the fludrocortisone dose in patients with 21β-hydroxylase deficiency with salt wasting
- compare the impact of sodium restriction and treatment with fludrocortisone on serum 17-OH-progesterone and testosterone concentrations in patients with 21β-hydroxylase deficiency
- evaluate the mineralocorticoid need in congenital hyperplasia caused by 11β-hydroxylase deficiency

These studies did not enable any conclusions to be drawn with regard to the efficacy of fludrocortisone in the treatment of primary and secondary adrenal insufficiency.

3.2. Tolerance

Few data have come out of the published studies because of the small number of patients included. However, because fludrocortisone has been used for more than 30 years in France in the form of a hospital preparation (60,000 tablets dispensed, or around 4,000 patients treated each year), its tolerance profile is well known. Its adverse effects are linked to its mineralocorticoid activity (water and sodium retention, hypokalaemia). These effects disappear after adjustment of the dosage (seek lowest effective dose). The most common adverse effects are: headache, muscle weakness, weight gain and oedema, hypokalaemia.
A pharmacovigilance unit for hospital preparations was created in 1994 at the Paris Hospitals central pharmacy. Since this unit was set up, fludrocortisone has been the subject of 5 spontaneous adverse event reports (2 cases of confusional disturbances, one case of diarrhoea, one case of hypokalaemia, one case of dizziness).

3.3. Conclusion

The 7 studies presented by the pharmaceutical company are not sufficient for an assessment of the efficacy of fludrocortisone, and ADIXONE in particular. However, the use of fludrocortisone as a medicinal substance is well established. It is indispensable to the management of primary adrenal insufficiency of any origin and of secondary adrenal insufficiency when mineralocorticoid replacement is justified.
Its tolerance is satisfactory when the dosage is adjusted. Its availability in a community setting will improve patient management.

4 TRANSPARENCY COMMITTEE CONCUSIONS

4.1. Actual benefit

Adrenal insufficiency is the result of a deficiency in the production of adrenal hormones (glucocorticoids and/or mineralocorticoids). In the absence of treatment, it leads to a marked deterioration in quality of life and can be life-threatening.
Fludrocortisone, in combination with a glucocorticoid, is an indispensable replacement therapy for primary adrenal insufficiency of any origin and for secondary adrenal insufficiency when mineralocorticoid replacement is justified.
Its efficacy/adverse effects ratio is high.

Public health benefit

Adrenal insufficiency in adults and children is a serious clinical situation which can be life-threatening in the absence of treatment, but which constitutes a low public health burden because of its rarity.

Improving the management of adrenal insufficiency constitutes a public health need which comes within the scope of established priorities (GTNDO*, Rare Diseases Plan, Plan for improving the quality of life of patients with chronic diseases).

Because it is a replacement for treatment with fludrocortisone which, although indispensable, already exists, the medicinal product ADIXONE is not expected to have an additional impact in terms of morbidity and mortality (episodes of acute adrenal insufficiency) and quality of life.

The medicinal product ADIXONE should not therefore be in a position to provide additional cover of the identified public health need.

Regarding the impact on the health system, the medicinal product ADIXONE will simplify patient access to care by its availability in a community setting.

Consequently, it is not expected that the medicinal product ADIXONE will have a public health benefit.

Alternative medicinal products do not exist.

The actual benefit of ADIXONE is substantial.

4.2. Improvement in actual benefit (IAB)

The medicinal product ADIXONE will replace the hospital preparation, "fludrocortisone AP-HP". It is indispensable to the management of adrenal insufficiency in adults and children. As such, the Transparency Committee considers that it retains the major therapeutic benefit of the hospital preparation.

4.3. Therapeutic use

The treatment of adrenal insufficiency is based on the administration of the deficient hormones:
- Hydrocortisone to correct the glucocorticoid deficiency
- Fludrocortisone to correct the mineralocorticoid deficiency when it is established

Use of fludrocortisone (ADIXONE)

Fludrocortisone is an aldosterone analogue. It must be combined systematically with hydrocortisone in the treatment of adrenal insufficiency because, at the usual dosages, its glucocorticoid activity is too weak for it to be used alone.
In primary adrenal insufficiency, fludrocortisone constitutes the indispensable replacement therapy..
Its indication is not systemtically in secondary adrenal insufficiency but depends on the presence and severity of mineralocorticoid deficiency (expert opinion).
ADIXONE is the first oral fludrocortisone-based pharmaceutical product to obtain a Marketing Authorisation in France and it replaces the hospital preparation which has been available since 1972. The Marketing Authorisation obtained, by making fludrocortisone available in a community setting, will simplify patient access to care.
Its dosage must be adjusted depending on arterial blood pressure, serum potassium and sodium levels and plasma renin activity which must be stay at the upper limit of the normal range. It must be used with caution in patients with severe, poorly controlled arterial hypertension and severe heart failure (cf. SPC).

4.4. Target population

According to the wording of the indication stated in the Marketing Authorisation, the target population for ADIXONE corresponds to patients with primary adrenal insufficiency of any origin or secondary adrenal insufficiency. Because the aetiologies of adrenal insufficiency are various: auto-immune, infection, tumour, bilateral adrenalectomy, prolonged corticosteroid therapy, etc., it is difficult to quantify precisely the population concerned by this indication.
According to the experts, the population most likely to benefit from treatment with ADIXONE is represented by patients with primary adrenal insufficiency, mainly Addison's disease, and those with a classic form (neonatal manifestation) of congenital adrenal hyperplasia.

The prevalence of Addison's disease estimated according to the available European epidemiological data is between 100 and 110 cases per million inhabitants, and the population with Addison's disease can therefore be estimated at between 6,400 and 7,000 patients.

The prevalence of the classical form of congenital hyperplasia, according to the Orphanet database, is estimated at 1 per 15,000 ie 4,200 patients.

In total, the theoretical target population for ADIXONE 50 µg scored tablet is around 10,000 patients (expert opinion).

For information, the population currently treated with the hospital fludrocortisone preparation is estimated, according to the AGEPS data, at 4,000 patients per year.

The real target population should therefore be between 4,000 and 10,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and/or on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions

Note: 10 µg and 100 µg presentations are being developed.

4.5.2. Reimbursement rate: 65%