

**Second Meeting of the Subcommittee of the Expert Committee on the
Selection and Use of Essential Medicines**

Geneva, 29 September to 3 October 2008

**Application for inclusion of Fludrocortisone tablets in the WHO
Model List of Essential Medicines for Children
(June 2008)**

Submitted by:

Royal Children's Hospital (RCH), Melbourne, Australia
National Institute of Child Health (NICH), Karachi, Pakistan
Caring & Living As Neighbours (CLAN), Australia

To:

Expert Committee on the Selection and Use of Essential Medicines
Children's Essential Medicines List
World Health Organization
Geneva

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*Detailed literature review pending

Introduction

The First List (October 2007) of the *WHO Model List of Essential Medicines for Children* does not include adrenal hormones nor synthetic substitutes (Section 18.1), however it does state “the Subcommittee noted the need for adrenal hormones and requested that appropriate products be reviewed for possible inclusion”¹.

This application for fludrocortisone tablets is made with particular reference to the critical role of fludrocortisone in the management of Congenital Adrenal Hyperplasia (CAH) in children. CAH is a genetically acquired (autosomal-recessive), chronic endocrine condition that is typically diagnosed in infancy or early childhood. Caused by an enzyme deficiency in the adrenal cortex, CAH is characterized by cortisol deficiency, aldosterone deficiency and hyperandrogenism. Oral fludrocortisone is the drug of choice for aldosterone replacement².

This request for the inclusion of fludrocortisone tablets in the *WHO Model List of Essential Medicines for Children* acknowledges the previous inclusion of: hydrocortisone powder for injection (Section 3 and 8.3); Prednisolone oral liquid and tablet (Section 3 and 8.3); and Dexamethasone for injection (Section 3 and 8.3). Unfortunately, none of these medications are appropriate routine daily treatments for CAH in children – although hydrocortisone for injection is a vital drug for the management of acute illness and adrenal crises in children with CAH².

The authors of this application are simultaneously submitting an application for hydrocortisone tablets, another essential medication for the management of CAH, necessary for glucocorticoid replacement.

1. Summary statement of the proposal for inclusion

This application is for the inclusion of fludrocortisone into the WHO Model List of Essential Medicines for Children. Fludrocortisone tablets are proposed for inclusion in the WHO Model List of Essential Medicines for Children for the treatment of Congenital Adrenal Hyperplasia (CAH) in childhood.

Fludrocortisone has been the mainstay in treatment for salt wasting variety of congenital adrenal hyperplasia and unfortunately it is the only formulation available to tackle this variant³, as no other synthetic adrenocortical steroid is comparable to its superior mineralocorticoid properties.

This proposal also acknowledges the similarly vital role fludrocortisone plays in the management of Addison’s Disease.

2. Name of the focal point in WHO supporting the application

No specific contact.

3. Name of the organisations consulted and supporting the application

Organisations consulted and writing application:

- Department of Endocrinology & Diabetes, Royal Children’s Hospital Melbourne, Australia.
- Medical Unit, National Institute of Child Health, Karachi, Pakistan.
- CLAN (Caring & Living As Neighbours) – Australian Non-Government Organisation (NGO)

Organisations Supporting the application (letters attached in Appendix 3):

1. CAH Support Network of New Zealand (CAHNZ Trust)
2. Indonesian Pediatric Society (Endocrinology Chapter)
3. CAH Support Group Network of the Philippines (CAHSAPI)
4. CARES Foundation (US based CAH Support Group Network)
5. Royal Children's Hospital International (RCHI)
6. Australian Addison's Disease Association Inc.
7. Association Surrénales (French Support Group)
8. The Philippines Society of Pediatric Metabolism & Endocrinology (PSPME)
9. National Institute of Child Health (NICH) – Karachi, Pakistan.
10. CLAN (Caring & Living As Neighbours)

(Letters attached in Section 14).

4. International nonproprietary name of the medicine

Fludrocortisone acetate (tablet).

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested for fludrocortisone acetate (tablets) as an individual medicine.

Fludrocortisone is a synthetic adrenocortical steroid which is given in combination with hydrocortisone in the management of congenital adrenal hyperplasia.

6. Information supporting the public health relevance

6.1 Definition of Congenital Adrenal Hyperplasia (CAH)

Congenital Adrenal Hyperplasia (CAH) is a family of inherited disorders of the adrenal cortex that impairs steroidogenic enzyme activity essential for cortisol biosynthesis^{4,5}. In over 90% of cases, CAH is due to 21-hydroxylase deficiency (21-OHD)⁶. This proposal will deal exclusively with 21-OHD, as it is the most common of all CAH disorders and the other types are very rare. Aldosterone production is interrupted in up to 66% of patients with 21-OHD – these children are identified as having salt-wasting (SW) CAH and require fludrocortisone replacement to survive⁷.

The goals of management of CAH are appropriate supra-physiologic replacement of glucocorticoids (as hydrocortisone in childhood, and necessary for all CAH patients), mineralocorticoid replacement (as fludrocortisone, for those with SWCAH), and suppression of the adrenal glands, thereby preventing inappropriate virilisation (caused by androgen excess) and achieving normal growth velocity and pubertal development². There is no cure for CAH. Treatment is required every day for life. Long-term inadequate treatment carries serious repercussions for both male and female children (such as progressive virilisation due to androgen excess, short stature, reduced fertility, psychological and social complications, and risk of adrenal crisis and death)^{8,9}. Additional glucocorticoid replacement is necessary during acute illness to prevent adrenal crisis (and death)².

6.2 Clinical Manifestation and Variability

The spectrum of disease in CAH ranges from the “classical, severe” salt wasting (SW) form to “classic, less severe” simple-virilizing (SV), to “mild, nonclassic” forms^{4,5}.

6.3 Epidemiology & Public Health Relevance

The commonest cause of *primary* adrenal insufficiency in childhood is **Congenital Adrenal Hyperplasia (CAH)** due to 21-hydroxylase deficiency.

The incidence of CAH has been demonstrated to vary markedly around the world. In western European countries and the USA, where newborn screening for CAH is provided, the incidence is in the range 1: 10,000-17,000 with an average of 1:14,000 births. Statistics from Newborn Screening trials show incidence rates of: 1 in 21270 live births in New Zealand; 1 in 15981 in North America, and 1 in 14970 in Europe. The incidence in Japan is 1 in 19111 live births. Significantly higher incidence rates have been demonstrated in certain populations, such as: rates of 1:5,933 live births in the Philippines; 1 in 5000 in Saudi Arabia; 1:5,000 in the Bahamas; 1:2,575 in India and 1:280 amongst Yupik Eskimos of Western Alaska^{10,11,12,13,14}. In many developing countries incidence figures have not been established, by virtue of the fact that no research in the area has been conducted. Anecdotally however, the numbers are significant: at the Endocrine Clinic at the National Hospital of Pediatrics in Hanoi, Vietnam, new patients are diagnosed at the rate of 2-3 per *week*; a Newborn Screening Trial in Ho Chi Minh City is expected to provide formal incidence figures for Vietnam in the foreseeable future¹⁵.

Prevalence is a separate issue, and not well documented due to insufficient CAH databases. Nonetheless, there are marked population differences in developed versus developing countries. The American CAH Support Group (CARES Foundation) has a national membership of around 4,900 families (population of USA just over 300 million). By comparison there are very low numbers of children known to have CAH in low income countries reflecting high mortality and missed diagnosis. A survey of Paediatric Endocrinologists from the Asia Pacific region suggested unaffordably available medication plays a major role in determining survival¹⁶. Examples of low income countries where prevalence figures are known include¹⁵: no children known to be living with CAH in Timor (population 2 million) or Laos (population 6.5million); perhaps 2 children known in Papua New Guinea (population 5.5million), around 100 children in the Philippines (population 80 million); and less than 200 children in Indonesia (population 200 million). Paradoxically there are around 400 children currently receiving treatment for CAH in Vietnam (population 80 million), but “loss to follow-up” figures are high.

Other causes of primary adrenal insufficiency in children include **Addison disease**, which in developing countries is caused by tuberculous destruction of the adrenals but in the rest of the world, is mainly due to autoimmune disease or rare genetic diseases such as adrenoleukodystrophy, lipoid adrenal hyperplasia and adrenal hypoplasia congenital. Patients with primary adrenal insufficiency require both a glucocorticoid and a mineralocorticoid.

Secondary adrenal insufficiency due to deficiency of pituitary ACTH occurs in congenital hypopituitarism (which is due to a congenital malformation such as holoprosencephaly, septo-optic dysplasia or interrupted pituitary stalk syndrome) or following the removal of a tumour such as a craniopharyngioma. Patients with secondary adrenal insufficiency are treated with a glucocorticoid alone, and do not need mineralocorticoid replacement.

7. Treatment details

7.1 Indications

Fludrocortisone Acetate is indicated as partial replacement therapy for primary and secondary adrenocortical insufficiency, as seen in Addison's disease and the salt wasting (SW) and simple virilizing (SV) variety of classical congenital adrenal hyperplasia¹⁷.

7.2 Dose

Initial Dose²: 0.05-0.3 mg/day *

Maintenance Dose²: 0.05-0.2mg/day *

*Dosage varies according to Sodium intake.

All children with classic CAH require treatment with fludrocortisone at diagnosis in the newborn period. The need for ongoing mineralocorticoid treatment beyond this period should be assessed (based on renin and BP measurements)¹⁸.

Standard fludrocortisone doses of 50-200mcg / day maintain plasma renin activity in the mid-normal range (depending on sodium intake). Requirements are usually higher in infancy, decreasing as the child gets older. Sodium chloride supplements are often needed in infancy, at 1-3gm/day (17-51mEq/day), distributed in several feedings^{2, 19}.

Doses can be split in half and given twice daily. The dose of fludrocortisone does not change during an adrenal crisis – only glucocorticoid doses need to be increased².

7.3 Duration

Treatment for CAH is life-long.

All classic CAH patients should be treated with fludrocortisone at the time of diagnosis in the newborn period and treatment is life-long but the requirement may spontaneously decrease with growing age²⁰.

7.4 Monitoring

During child-hood, routine medical review and blood tests are ideally used to ensure the glucocorticoid and mineralocorticoid replacement doses are satisfactory.

Mineralocorticoid replacement is monitored by Blood Pressure (BP) readings, plasma renin activity and electrolytes. During infancy blood tests every 3 months (PRA or direct renin) are indicated, stretching out to 4-12 monthly testing as the child grows older^{2,20}.

8. Summary of comparative effectiveness in a variety of clinical settings

Neonates with the salt wasting (SW) form of CAH exhibit adrenal crisis during the first four weeks of life, peaking at approximately 3 weeks of age. This manifests as poor feeding, vomiting, loose stools or diarrhea, weak cry, failure to thrive, dehydration and lethargy. These symptoms may not be evident until serum sodium concentrations are below 125 mEq/L. If untreated, circulatory collapse, shock, and death are inevitable. Permanent brain injury attributable to shock, such as lower cognitive scores and learning disabilities are observed in some with the salt wasting form⁵.

Below is a comparison of salt retention of different corticosteroids showing Relative Biologic Potencies of Synthetic Steroids in Bioassay Systems²⁰.

STEROID	SALT RETENTION
Cortisol	1
Prednisolone	0.75
Methylprednisolone	0.5
Fludrocortisone	125
Triamcinolone	0
Dexamethasone	0

In 1977, some researchers demonstrated that patients considered to have SVCAH may also suffer from subtle impairment of aldosterone biosynthesis and recommended mineralocorticoid treatment for these patients²¹. This view was reinforced in a retrospective study in 2003 which proved that appropriately treated classical congenital adrenal hyperplasia patients showed better outcomes²². Therefore early diagnosis, the use of more physiological cortisol equivalent dosages during the first years of life, and the extension of mineralocorticoid therapy to all genetically classical patients can improve the auxological outcome of congenital adrenal hyperplasia patients.

*Detailed literature review pending

9. Summary of comparative evidence on safety

Fludrocortisone is the only drug available to tackle the effects of high plasma rennin activity which inevitably leads to salt wasting, life threatening adrenal crisis and sudden death. As per consensus, fludrocortisone is recommended in all cases of classical congenital adrenal hyperplasia (salt wasting and simple virilizing) as it considerably helps in lowering the required dosage of glucocorticoids, thus lowering the side effects of treatment².

The mortality rate also drops from a staggering 11.9% (untreated) to 4.3% for treated patients²³.

Most of the adverse side effects like hypertension, edema, cardiac enlargement, and congestive heart failure are caused by the drug's mineralocorticoid activity. These side effects are usually due to over-dosage over long periods of time. When it is used in small recommended doses patients usually don't experience these side effects¹⁷.

Clearly the benefits of fludrocortisone outweigh its adverse effects. Until further new treatments are proposed and clinical trials available, there is no alternative to fludrocortisone usage in managing the salt wasting variety of congenital adrenal hyperplasia.

*Detailed literature review pending

10. Summary of available data in comparative cost within the pharmacological class or therapeutic group

Range of costs of the proposed medicine

In Australia fludrocortisone acetate (Florinef®) tablets are available at a cost of AUD \$5.80 per 100 tablets. This gives an approximate cost of AUD0.06 per tablet.

No comparative medications available to compare costs.

Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

On average a child with SW CAH will need 1 tablet per day for their whole life. The cost of this treatment would amount to around \$21.17 per annum per child. This treatment is life-saving. Without it, the child will die.

*Detailed literature review pending

11. Summary of regulatory status of medicine

Fludrocortisone acetate is registered as Florinef® in Australia, New Zealand, UK and USA.

Fludrocortisone acetate is not registered in many countries (usually low-income), including Vietnam, the Philippines, Indonesia, Laos, Pakistan, Bangladesh, Cambodia, Burma, Ethiopia, Mexico or Haiti. A generic brand of fludrocortisone is available in India (Manufactured by Samarth Pharma).

12. Availability of pharmacopoeial standard

British Pharmacopoeia

13. Proposed text for the WHO Model Formulary

Fludrocortisone acetate:

Synthetic adrenocortical steroid

Tablet contains: 0.1mg fludrocortisone acetate/tablet
(Available in bottle of 100 tablets/bottle)

Inactive ingredients: lactose, dicalcium phosphate, corn starch, magnesium stearate, talc and sodium benzoate.

Indications²⁴:

Partial replacement in primary and secondary adrenocortical insufficiency in Addison's disease and in both salt wasting (SW) and simple virilizing (SV) forms of classical congenital adrenal hyperplasia.

Contraindications²⁴:

Hypersensitivity to any of the ingredients.
Systemic infections unless specific anti-infective therapy is involved.
Should not be used in patients with congestive heart failure.

Precautions²⁴:

- Because of its marked effect on sodium retention, the use of Fludrocortisone in the treatment of conditions other than those indicated is not advised.
- As fludrocortisone is a potent mineralocorticoid both the dosage and salt intake should be carefully monitored to avoid development of hypertension, edema or weight gain. Periodic checking of serum electrolytes is highly advisable during prolonged therapy.
- The glucocorticoid side effects may occur but can be reduced by decreasing the dosage. The lowest effective dose is highly recommended.

Dosage²:

Initial Dose: 0.05-0.3 mg/d

Maintenance Dose: 0.05-0.2mg/d

*Dosage varies according to Sodium intake in SW CAH.

Adverse Effects²⁴:

Where adverse reactions occur, they are usually reversible on cessation of therapy. The incidence of predictable side-effects, including hypothalamic-pituitary-adrenal suppression correlate with the relative potency of the drug, dosage, timing of administration and duration of treatment.

Patients should be watched closely for the following adverse reactions which may be associated with any corticosteroid therapy:

- Anti-inflammatory and immunosuppressive effects: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (See Warnings and Precautions).
- Fluid and electrolyte disturbances: sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, cardiac arrhythmias or ECG changes due to potassium deficiency, hypokalaemic alkalosis, increased calcium excretion and hypertension.
- Musculoskeletal: muscle weakness, fatigue, steroid myopathy, loss of muscle mass, osteoporosis, avascular osteonecrosis, vertebral compression fractures, delayed healing of fractures, aseptic necrosis of femoral and humeral heads, pathological fractures of long bones and spontaneous fractures, tendon rupture.
- Gastrointestinal: dyspepsia, peptic ulcer with possible subsequent perforation and haemorrhage, pancreatitis, abdominal distension and ulcerative oesophagitis, candidiasis.
- Hypersensitivity: Anaphylactic reactions, angiodema, rash, pruritus and urticaria, particularly where there is a history of drug allergies.
- Dermatologic: impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, purpura, striae, hirsutism, acneiform eruptions, lupus erythematosus-like lesions and suppressed reactions to skin tests.
- Neurological: euphoria, psychological dependence, depression, insomnia, convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, neuritis or paraesthesias and aggravation of pre existing psychiatric conditions and epilepsy.
- Endocrine/metabolic: menstrual irregularities and amenorrhoea; development of the Cushingoid state; suppression of growth in childhood and adolescence; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (eg. trauma, surgery or illness); decreased carbohydrate tolerance; manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycaemic agents in diabetes, weight gain. Negative protein and calcium balance. Increased appetite.
- Ophthalmic: posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.
- Others: necrotising angiitis, thrombophlebitis, thromboembolism, leucocytosis, insomnia and syncopal episodes.
- Withdrawal Symptoms and Signs: On withdrawal, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss may occur. Too rapid a reduction in dose following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death.

Drug Interactions²⁴:

- Amphotericin B injection and potassium-depleting agents: Patients should be observed for hypokalemia.
- Anticholinesterases: Effects of anticholinesterase agents may be antagonised.
- Anticoagulants, oral: Corticosteroids may potentiate or decrease anticoagulant action. Patients receiving oral anticoagulants and corticosteroids should therefore be closely monitored.
- Antidiabetics: Corticosteroids may increase blood glucose; diabetic control should be monitored, especially when corticosteroids are initiated, discontinued, or changed in dosage.
- Antihypertensives, including diuretics: corticosteroids antagonise the effects of antihypertensives and diuretics. The hypokalaemic effect of diuretics, including acetazolamide, is enhanced.
- Anti-tubercular drugs: Isoniazid serum concentrations may be decreased.
- Cyclosporin: Monitor for evidence of increased toxicity of cyclosporin when the two are used concurrently.
- Digitalis glycosides: Co-administration may enhance the possibility of digitalis toxicity.
- Oestrogens, include oral contraceptives: Corticosteroid half-life and concentration may be increased and clearance decreased.
- Hepatic Enzyme Inducers (e.g. aminoglutethemide, barbiturates, carbamazepine, phenytoin, primidone, rifabutin, rifampicin): There may be increased metabolic clearance of Florinef. Patients should be carefully observed for possible diminished effect of steroid, and the dosage should be adjusted accordingly.
- Human growth hormone: The growth-promoting effect may be inhibited.
- Ketoconazole: Corticosteroid clearance may be decreased, resulting in increased effects.
- Nondepolarising muscle relaxants: Corticosteroids may decrease or enhance the neuromuscular blocking action.
- Nonsteroidal anti-inflammatory agents (NSAIDs): Corticosteroids may increase the incidence and/or severity of GI bleeding and ulceration associated with NSAIDs. Also, corticosteroids can reduce serum salicylate levels and therefore decrease their effectiveness. Conversely, discontinuing corticosteroids during high-dose salicylate therapy may result in salicylate toxicity. Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia.
- Thyroid drugs: Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in adrenocorticoid dosage.
- Vaccines: Neurological complications and lack of antibody response may occur when patients taking corticosteroids are vaccinated.

Over dosage²⁴:

A single large dose should be treated with plenty of water by mouth. Careful monitoring of serum electrolytes is essential, with particular consideration being given to the need for administration of potassium chloride and restriction of dietary sodium intake.

14.1 Appendix 1 – Letters from organisations supporting this application

14.1.1 CAH Support Group of New Zealand (CAHNZ Trust)

CAHNZ Trust
P.O.Box 29-545
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Ilam
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New Zealand
Tel: +64 3 3584 507
Fax: +64 3 3584 506
Email: CAHNZ@snap.net.nz



Expert Committee on the Selection and Use of Essential Medicines
Children's Essential Medicines List
World Health Organization
Geneva

24th May 2008

To Whom It May Concern,

For over eleven years I have run a national (New Zealand) support group for individuals and families whose children are affected by the endocrine disorder, Congenital Adrenal Hyperplasia. Recently achieving charitable status, our Trust now represents around seventy people with this condition, whose ages range from 0-40 years. Over a hundred thrice-yearly newsletters are sent out by our organization to members and health professionals. This support group enjoys good standing in the medical community and is highly valued by its members as a source of information and support. Our group is also affiliated with a number of sister organizations both nationally and internationally and is listed as the official New Zealand contact on many other websites.

On behalf of the CAHNZ Trust and its members, I am writing to state our wholehearted support for the inclusion of the medications hydrocortisone and fludrocortisone into the WHO Children's Essential Medicines List. Our reasons are very simple.

The daily taking of corticosteroids is a non-negotiable issue for CAH-affected children and adults. Without access to a regular supply of this medication these people would die. Those with affected family members are reminded of this daily. Having access to reliable, quality medicine continues to be a source of ongoing anxiety to many New Zealanders, despite the fact that we live in a part of the world where free, quality health care is available. When there is a worldwide shortage of medication, or when medication is reformulated in some way (alterations to colour, shape, or storage conditions), these changes add stress to lives which already carry extra health burdens. A small domestic incident such as dropping a container of

hydrocortisone syrup (specially formulated by designated pharmacists), medication being in lost luggage whilst travelling, or being on holiday in a remote area when getting sick, highlight some of the issues that members have to contend with in managing their daily medication regime.

On behalf of our Trust and members I raise these issues for your consideration and sincerely request your support in designating these medications in the children's essential medicines list. We fully back adoption of this proposal.

Thank you for your consideration of this letter.

Yours sincerely,

Helen Mann

CAHNZ Founder & Director

14.1.2 Indonesian Pediatric Society Endocrinology Chapter



IKATAN DOKTER ANAK INDONESIA (I.D.A.I)
CENTRAL EXECUTIVE BOARD
INDONESIAN PEDIATRIC SOCIETY
Endocrinology Chapter

Jl. Salemba 6, Jakarta Pusat – 10430, Indonesia
Telp (62-021) 3100674, 3148610 FAX (62-021) 3913982



Jakarta, 25 May 2008

To:
Expert Committee on the Selection and Use of Essential Medicines
Children's Essential Medicines List
World Health Organization
Geneva

To Whom it May Concern,

My name is Aman B Pulungan, and I am presently the Chairman of Endocrinology Chapter, Central Board of Indonesian Pediatric Society. On behalf of the organization, I would like to request your consideration to include the hydrocortisone and fludrocortisone in the WHO Children's essential medicines list and to provide recommendation to our Government to make the above medicines available for CAH children in Indonesia.

Based on the current statistic, there are approximately 15,000 CAH children detected, and the number continues to escalate. The increase is approximately ranges from 327 to 409 cases each year. Most of the children come from lower to middle group of income with annual earning range from USD 500 to USD 40,000. Those children have not received proper medication and some received irregular medication due to unavailability of the drugs in the country. Those who come from upper income group normally purchased the medicine overseas while the remaining mostly expect and receive donation from the organization such as CLAN. These issues may create potential discontinuity of the supply, which will have great impact on the future survival of CAH children in Indonesia.

Due to the increasing number of CAH children, it is our main concern to ensure these children will receive proper and continued medication for life times. Thus, it is essential to have the recommended drugs available in our country and to include these medicines in the WHO Children's Essential Medicines List. Any information pertaining CAH children are available, if needed, to support the inclusion of these medicines in the WHO list.

As mentioned earlier, there are registered 245 CAH children spread throughout the archipelago. Their health conditions as well as their economic conditions are deteriorating as there is no sufficient drug supply and due to high price of the medicines. Doctors are also unable provide proper treatment without prescribing these drugs and often face difficulties to find alternate medications. Parents feel they are unable to speak for


themselves and/ or make recommendation to the Government without support from our organization. On the hand, we need WHO support to convince our Government that these drugs are needed.

There are a number of CAH children detected who have not received any medication at all. These children live in number of region of Indonesia and ranging from the age of 3 months to 18 years where medicines are out of their reach. As highlighted above, those children CAH we have detected to date are in dire need for the hydrocortisone and fludrocortisone and their survivals are very much dependent on these drugs.

In closing, we would highly appreciate your consideration and support to include the above medicines in WHO Children's essential medicines list. It is our mission to help maintain and improve the health our future generation including CAH children. CAH children also deserve happy life and bright future like any other healthy children in the world.

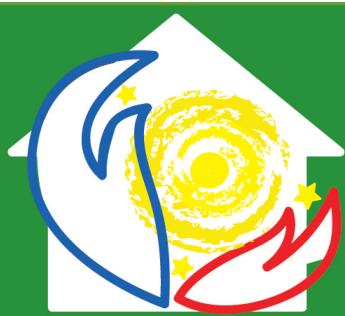
We thank you for your kind attention and cooperation.

Yours Sincerely

A handwritten signature in black ink, reading "Aman B. Pulungan". The signature is written in a cursive style with a long, sweeping underline that extends to the left.

Aman B. Pulungan MD
Chairman of Endocrinology Chapter

14.1.3 CAH Support Group of the Philippines (CAHSAPI)



CAHSAPI :: CAH Support and Advocacy PHILIPPINES

29 May 2008

To Whom It May Concern:

Introduction of yourself and organisation. Brief indication of number of children with CAH in your country / care (if relevant)

Greetings! My name is Alain Yap and I write to you in behalf of CAHSAPI - the first Philippine Support Group for families dealing with CAH with temporary office located inside the Philippine General Hospital. My wife and I have a daughter who was diagnosed with Congenital Adrenal Hyperplasia or CAH in 2004. Words can barely express the difficulties facing us then. But the threat of death only hardened our resolve to abandon everything else and dedicate our lives to ensure that she will live. As we were able to gather the help we needed, we also were exposed to the plight of other children with CAH who come from poor families and despite the added responsibility and likewise limited resources, I accepted the prodding of doctors when asked to head this group. To date, our members now number around 80 and expecting more as newborn screening in the country continues to detect those born with CAH.

Our group is primarily composed of indigent families who can barely afford their daily needs and do not have the resources to handle the additional burden brought about by the condition. As the medicines we need for our children are not available locally, we were fortunate to receive help from outside sources in the form of medicines which we distribute to members for a nominal fee - which we also use for emergency purchases of additional supplies. Other group activities concern parenting, continuous education for parents regarding CAH and required forms of treatment.

Indication of your support for the inclusion of hydrocortisone and fludrocortisone in the WHO Children's Essential Medicines List

Why you feel these drugs should be included:

Quite simply, these 2 drugs help keep my child and children with CAH alive. Placing them on the list would give treatment of CAH the importance and priority it needs and would work towards greater understanding of the condition, most of the populace have not even heard exists.

Please include examples from your country on difficulties families face if relevant

Both drugs are not available locally and puts persons with CAH at unnecessary and uncertain risk everyday. It does not help that government imposes duties and tax on such medicine donations during importation, depleting the funds that would be best used on getting more medicines as working on getting the exemptions is almost a futile and effort intensive exercise. Moreover, the families affected belong to low or no-income brackets. No access to those drugs is almost tantamount to letting the babies suffer a slow death.

Any other points you would like to make!

CAH requires a lifetime of treatment and medications. It is a burden which we wish not upon anyone. Access to the medicines on a daily basis remains our priority and any step that would help bring us these medicines also bring us hope that despite all the difficulties, we will overcome.

Yours Sincerely,

Alain Benedict Yap
President

14.1.4 CARES Foundation (US based CAH Support Group Network)



Chief Executive Officer

Kelly Rosso Leight, Esq.

Chief Operating Officer

Meryl I. Stone

Program Manager

Suzanne R. Levy

Development Director

Ellie Avitan

Public Affairs

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(City of Los Angeles)

June 4, 2008

To Whom It May Concern:

Since 2001, CARES Foundation, Inc. has been committed to improving the lives of families and individuals affected by Congenital Adrenal Hyperplasia (CAH) through proactively advancing research for better understanding of CAH, better treatments and a cure; educating the public and healthcare professionals about all forms of CAH; advocating for universal newborn screening; and providing support services and resources vital to the CAH community worldwide. Our national membership includes over 4900 families. Internationally, we have close to 250 families registered in our membership.

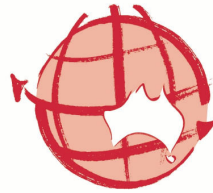
We are writing in strong support of the inclusion of hydrocortisone and fludrocortison in the WHO Children's Essential Medicines List. These medications are vital to the survival of people living with CAH. Without these medications children with CAH will, and do, die.

Many families with little or no insurance have difficulty obtaining these medications that keep their children alive. Indeed, even families with the best insurances are sometimes not covered for these medications. It is for these reasons that CARES Foundation is in support of including hydrocortisone and fludrocortisones in the Children's Essential Medicines List.

Sincerely,

Suzanne Levy
Program Manager

14.1.5 Royal Children's Hospital International (RCHI)



RCHI
Royal Children's Hospital
International

29 May 2008

Expert Committee on the Selection and Use of Essential Medicines
Children's Essential Medicines List
World Health Organization
Geneva

To Whom it May Concern,

For the past 30 years, I have been providing specialist care for children with congenital adrenal hyperplasia (CAH) at the Endocrine Clinic at the Royal Children's Hospital Melbourne. Since 1995, I have made over 35 visits to the National Hospital of Pediatrics in Hanoi. I soon became aware that children with CAH in Hanoi did not have access to hydrocortisone or fludrocortisone. Instead, they were receiving prednisolone alone, and when they experienced adrenal crisis (which they did quite frequently) they had to come to the central hospital for an injection of desoxycorticosterone – DOC – and then go home on prednisolone to wait for the next crisis. Not surprisingly, the death rate was horrendous and life for the survivors was terrible, with stunted growth and Cushingoid appearance. Currently NHP has 350 patients with CAH in the Endocrine Clinic.

I strongly advocate the inclusion of hydrocortisone and fludrocortisone in the Essential Medicines List for Children.

Hydrocortisone is a short acting glucocorticoid that has been shown to have a smaller inhibitory effect on growth than prednisolone. It has some mineralocorticoid action as well, which is beneficial in salt-losing congenital adrenal hyperplasia and Addison's disease. It is recommended as the drug of choice in international consensus guidelines on the treatment of CAH. Fludrocortisone is essential for the treatment of mineralocorticoid deficiency and there is no substitute.

Since children in Hanoi gained access to donated supplies of hydrocortisone and Florinef, mortality has fallen to zero. This is dramatic testament to the benefit that flows from having these two essential medicines.

Yours faithfully,

Professor Garry L Warne,
Director, RCHI
and Senior Endocrinologist, Royal Children's Hospital, Melbourne
Professor Garry L Warne MBBS FRACP

Director, Royal Children's Hospital International

The Royal Children's Hospital, Melbourne

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Australia

14.1.6 Australian Addison's Disease Association Inc.

14.1.7 Association Surrénales (French Support Group)

14.1.8 Philippines Society of Pediatric Metabolism and Endocrinology (PSPME)

14.1.9 National Institute of Child Health, Karachi, Pakistan

14.1.10 Caring & Living As Neighbours (CLAN)

**14.2 Appendix 2 - Consensus Statement on 21OHD
Management**

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