

Nagorno-Karabakh (Republic of Artsakh): humanitarian crisis and endocrine drug shortages

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Joint Statement from the European Society of Endocrinology (ESE), the European Society for Paediatric Endocrinology (ESPE), the Armenian Association of Paediatric Endocrinologists and the Armenian Association of Endocrinology.

To whom it may concern

The European Society of Endocrinology and the European Society for Paediatric Endocrinology consulted with their partner societies in Armenia and are hereby highlighting the following needs with regard to urgent medical drug supply, required to secure the continued care of patients with endocrine disease in Nagorno-Karabakh (Republic of Artsakh).

Insulin for the treatment of diabetes – this is life critical. Patients with diabetes mellitus, particularly type 1 diabetes, need unrestricted access to insulin. A shortage of insulin is immediately life-threatening. The supply of long and short acting insulins has to be accompanied by adequate supplies of **glucose test strips and glucose measuring devices**, as the blood-glucose values form the cornerstone of diabetes self-management. Also, in case of acute stress, infection or trauma and inadequate diet (food supply being difficult during war) the insulin dose may need adaptations and adequate glycemic control is an important healing factor.

Glucagon may be required in patients with diabetes who have too low blood sugar levels (hypoglycemia), as it helps to restore normal blood levels. Hypoglycemic episodes in diabetic patients taking glucose-lowering medications, namely insulin or sulfonylureas, are typically treated with oral glucose. However, glucagon preparations for intramuscular, subcutaneous and/or intranasal application may be particularly important to treat episodes of severe and potentially life-threatening hypoglycemia, where patients are either unable to treat themselves or glucose intake by mouth has not been successful.

The substitution with **hydrocortisone/cortisone acetate/prednisolone** for patients with adrenal insufficiency is critical. Cortisol is the hormone that allows the body to respond to stress situations. If the body doesn't produce this itself, and if the patient doesn't receive daily substitution with hydrocortisone, cortisone acetate or prednisolone, this will lead to adrenal crisis and death within 24 to 48 hours if not immediately treated with high dose injections of hydrocortisone. Hydrocortisone and cortisone acetate are the first choice product (identical or similar to the natural hormone), whereas prednisolone is a second choice product (chemically related compound) for these patients. In case of adrenal crisis, hydrocortisone injections are needed (if not available prednisolone or methylprednisolone should be used).

Also **Fludrocortisone** is a critical hormone that needs to be administered in the case of primary adrenal insufficiency (also known as Addison's disease). Fludrocortisone is particularly relevant in controlling the amount of salt (sodium) and fluids in the body, and it works by decreasing the

amount of sodium that is lost (excreted) in the urine. It also affects the strength of heart muscle and helps the body to cope with stress (temperature, pain, fear, anxiety, and illness). When omitted, patients are at particular risk of severe hyponatremia, hyperkalemia, hypovolemia, dehydration, hypotension, shock and ultimately death.

Levo-thyroxine is used as substitution therapy in patients with (congenital) hypothyroidism, the substitution for autoimmune thyroiditis (Hashimoto disease), after thyroidectomy (surgical removal of the thyroid gland), for the prevention of a recurrence of thyroid cancer, in patients with disease of Graves-Basedow in combination with thyreostatics to maintain a normal thyroid balance. Absence of treatment leads to severe hypothyroidism that might require intensive care unit support as it could be lethal after 2 to 3 weeks due to coma.

Antithyroid medications, such as carbimazole, methimazole or propylthiouracil, are drugs that inhibit the production and release of thyroid hormones, and thus are critical for the management of patients with overactive thyroid gland, i.e. hyperthyroidism and thyrotoxicosis. Thyrotoxicosis is a clinical state of inappropriately high levels of circulating thyroid hormones (T3 and/or T4) in the body, which render the patients with a wide range of symptoms such as weight loss, palpitations, heart racing, tremors, anxiety, irritability, increased perspiration, muscular weakness, skin problems, among others. Severe hyperthyroidism might be life-threatening, thus treatment with antithyroid medications should be promptly administered.

Desmopressin tablets and spray are used in patient with diabetes insipidus. This is a condition that causes the body to lose too much fluid and become dehydrated. Lack of treatment in patients non able to compensate with large amount of water (more than 4 liters/day) leads to dehydration in less than 24 hours and hypernatremia that could be lethal. Because water supply can be problematic during humanitarian crises this is even more important for the diabetes insipidus patients.

Gonadotrophin Releasing Hormone analogues (GnRHa), including **Triptorelin, Leuprolide, Goserelin**, etc, are used to treat early-onset puberty occurring at a very young age (before 8 years in girls and 9 years in boys), i.e., Precocious Puberty. The effective treatment of early puberty requires uninterrupted access to triptorelin until a normal pubertal age has been reached. In adult patients, GnRHa are used in the treatment of prostate cancer in men, while in women, GnRHa are used to treat breast cancer, uterine fibroids, or endometriosis (a condition in which the tissue that normally lines the uterus (endometrium) grows in other places in the abdomen).

Cabergoline and **bromocriptine** are dopamine agonist medications aimed to treat high levels of prolactin (hyperprolactinemia), a hormone that can cause infertility, sexual problems, galactorrhoea, and bone loss. The main cause of pathological hyperprolactinemia is a prolactinoma, which is a benign tumour of the pituitary gland, however it is often large and compress adjacent structures like the optic chiasm, leading to mass-effect symptoms such as visual field defects and headache. Hence, such medications are important not only to decrease the serum levels of prolactin and restoring the gonadal and reproductive function, but also to control the tumour size and growth, particularly relevant for large or giant prolactinoma cases. Cabergoline and bromocriptine are commercialized under the brand names of Dostinex® and Parlodel®, respectively.

Somatostatin analogues (octreotide, lanreotide and pasireotide) are synthetic versions of the natural hormone somatostatin, which inhibits the release of growth hormone and other hormones from the endocrine system. It is widely used to treat various conditions, such as gastroentero-pancreatic Neuroendocrine Tumours (NETS), as well as for the treatment of patients with functioning

pituitary tumours, namely for acromegaly, thyrotrophinomas or Cushing's disease. Moreover, octreotide is used to treat various other conditions such as bleeding from oesophageal varices, gastro-intestinal ulcers, gastritis and pancreatitis.

Dapagliflozin (Forxiga®) and sitagliptin (Januvia®) are oral antidiabetic medications belonging to the drug classes of sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase 4 inhibitors (DPP-4i), respectively. Both of these medications are effective in lowering blood sugar levels in adults with type 2 diabetes, and help achieving a good metabolic control in such patients. Dapagliflozin may also be used for treating heart failure or chronic kidney disease. Other examples of SGLT-2i include canagliflozin, empagliflozin and ertugliflozin, whereas vildagliptin, linagliptin, saxagliptin and alogliptin are other examples of medications belonging to the family of DPP-4i).

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