Statement of Principles concerning CUSHING SYNDROME (Balance of Probabilities) (No. 44 of 2018)

The Repatriation Medical Authority determines the following Statement of Principles under subsection 196B(3) of the Veterans' Entitlements Act 1986.

Dated 27 April 2018

The Common Seal of the Repatriation Medical Authority was affixed to this instrument at the direction of:

[Signature]

Professor Nicholas Saunders AO
Chairperson
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1 Name
This is the Statement of Principles concerning Cushing syndrome (Balance of Probabilities) (No. 44 of 2018).

2 Commencement
This instrument commences on 28 May 2018.

3 Authority
This instrument is made under subsection 196B(3) of the Veterans’ Entitlements Act 1986.

4 Revocation
The Statement of Principles concerning Cushing’s syndrome No. 34 of 2009 made under subsection 196B(3) of the VEA is revoked.

5 Application
This instrument applies to a claim to which section 120B of the VEA or section 339 of the Military Rehabilitation and Compensation Act 2004 applies.

6 Definitions
The terms defined in the Schedule 1 - Dictionary have the meaning given when used in this instrument.

7 Kind of injury, disease or death to which this Statement of Principles relates

(1) This Statement of Principles is about Cushing syndrome and death from Cushing syndrome.

Meaning of Cushing syndrome

(2) For the purposes of this Statement of Principles, Cushing syndrome means an endocrine disorder resulting from an excess of endogenous or exogenous glucocorticoids.

Note: Features of Cushing syndrome may include proximal muscle weakness, facial plethora, wasting of the extremities with increased fat in the abdomen (centripetal fat) and face (“moon facies”), wide (> 1 cm) purplish striae, bruising with no obvious trauma, supraclavicular fat pads and dorsocervical fat pad (“buffalo hump”).

(3) While Cushing syndrome attracts ICD-10-AM code E24.0, E24.2, E24.3, E24.8 or E24.9, in applying this Statement of Principles the meaning of Cushing syndrome is that given in subsection (2).

(4) For subsection (3), a reference to an ICD-10-AM code is a reference to the code assigned to a particular kind of injury or disease in The International Statistical Classification of Diseases and Related Health
Death from Cushing syndrome

(5) For the purposes of this Statement of Principles, Cushing syndrome, in relation to a person, includes death from a terminal event or condition that was contributed to by the person's Cushing syndrome.

Note: terminal event is defined in the Schedule 1 – Dictionary.

8 Basis for determining the factors

On the sound medical-scientific evidence available, the Repatriation Medical Authority is of the view that it is more probable than not that Cushing syndrome and death from Cushing syndrome can be related to relevant service rendered by veterans or members of the Forces under the VEA, or members under the MRCA.

Note: MRCA, relevant service and VEA are defined in the Schedule 1 – Dictionary.

9 Factors that must exist

At least one of the following factors must exist before it can be said that, on the balance of probabilities, Cushing syndrome or death from Cushing syndrome is connected with the circumstances of a person's relevant service:

(1) having a specified condition at the time of the clinical onset of Cushing syndrome;

Note: specified condition is defined in the Schedule 1 - Dictionary.

(2) having glucocorticoid therapy as specified before the clinical onset of Cushing syndrome, and where the glucocorticoid therapy as specified has ceased or decreased, the last dose of the therapy was received within the 30 days before the clinical onset of Cushing syndrome;

Note: glucocorticoid therapy as specified is defined in the Schedule 1 - Dictionary.

(3) being treated with medroxyprogesterone acetate or megestrol acetate for a malignant disease or human immunodeficiency virus infection:

(a) for at least four weeks before the clinical onset of Cushing syndrome; and

(b) where treatment has ceased, the clinical onset of Cushing syndrome has occurred within 30 days of cessation;

(4) inability to obtain appropriate clinical management for Cushing syndrome.
10 Relationship to service

(1) The existence in a person of any factor referred to in section 9, must be related to the relevant service rendered by the person.

(2) The factor set out in subsection 9(4) applies only to material contribution to, or aggravation of, Cushing syndrome where the person's Cushing syndrome was suffered or contracted before or during (but did not arise out of) the person's relevant service.

11 Factors referring to an injury or disease covered by another Statement of Principles

In this Statement of Principles:

(1) if a factor referred to in section 9 applies in relation to a person; and

(2) that factor refers to an injury or disease in respect of which a Statement of Principles has been determined under subsection 196B(3) of the VEA;

then the factors in that Statement of Principles apply in accordance with the terms of that Statement of Principles as in force from time to time.
Schedule 1 - Dictionary

Note: See Section 6

1 Definitions

In this instrument:

**adrenal neoplasm** means a primary neoplasm, either benign (adenoma) or malignant (carcinoma), arising from the adrenal gland.

**Cushing syndrome**—see subsection 7(2).

**equivalent glucocorticoid therapy** means a glucocorticoid in the following table, at the doses specified in the table, or a therapeutically equivalent dose of another glucocorticoid:

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Minimum cumulative dose (milligram)</th>
<th>Minimum average rate (milligram/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>betamethasone</td>
<td>45</td>
<td>1.5</td>
</tr>
<tr>
<td>cortisone</td>
<td>1 875</td>
<td>62.5</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>55</td>
<td>1.8</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>paramethasone</td>
<td>150</td>
<td>5</td>
</tr>
<tr>
<td>prednisolone</td>
<td>375</td>
<td>12.5</td>
</tr>
<tr>
<td>prednisone</td>
<td>375</td>
<td>12.5</td>
</tr>
<tr>
<td>triamcinolone</td>
<td>300</td>
<td>10</td>
</tr>
</tbody>
</table>

**equivalent inhaled glucocorticoid** means:

(a) 2 000 micrograms of beclometasone;
(b) 1 600 micrograms of ciclesonide;
(c) 2 500 micrograms of fluticasone propionate;
(d) 1 000 micrograms of fluticasone furoate;
(e) 10 000 micrograms of triamcinolone; or
(f) a therapeutically equivalent dose of another inhaled glucocorticoid.

**glucocorticoid therapy as specified** means:

(a) applying a high or very high potency topical glucocorticoid to at least 30% of total skin surface area, daily, for at least six months; or
(b) inhaling at least 4 000 micrograms of budesonide, or equivalent inhaled glucocorticoid, daily, for at least six months; or
(c) taking:
   (i) hydrocortisone, orally or by injection:
       (A) to a cumulative dose of at least 1 500 milligrams; and
       (B) at a minimum dose rate averaging 50 milligrams per day, or
   (ii) equivalent glucocorticoid therapy, orally or by injection; or
(d) using a glucocorticoid concurrently with a drug, daily, for at least 4 weeks, where that drug can inhibit the activity of the metabolising enzyme cytochrome P450 3A4 by at least 30% (moderate to strong inhibition); or...
(e) using a glucocorticoid concurrently with a drug from the specified list of drugs, daily, for at least four weeks; or
(f) using a clobetasol containing oral preparation, daily, for at least four weeks; or
(g) using glucocorticoid containing enemas, daily, for at least six months.

Note: equivalent glucocorticoid therapy, equivalent inhaled glucocorticoid, high or very high potency topical glucocorticoid and specified list of drugs are also defined in the Schedule 1 – Dictionary.

high or very high potency topical glucocorticoid means:
(a) betamethasone dipropionate 0.05%;
(b) betamethasone valerate 0.1%;
(c) clobetasol propionate 0.05%;
(d) diflucortolone valerate 0.1%;
(e) fluocinolone acetonide 0.025%;
(f) methylprednisolone 0.1%;
(g) mometasone 0.1%;
(h) triamcinolone acetonide 0.5%; or
(i) another topical glucocorticoid of equivalent potency.


neuroendocrine neoplasm means a non-pituitary neoplasm that secretes polypeptides functionally equivalent to adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone (CRH), and includes oat cell or small cell lung carcinoma, carcinoid tumour, islet cell tumour, tumours of the thymus, medullary carcinoma of the thyroid, and phaeochromocytoma.

relevant service means:
(a) eligible war service (other than operational service) under the VEA;
(b) defence service (other than hazardous service and British nuclear test defence service) under the VEA; or
(c) peacetime service under the MRCA.

Note: MRCA and VEA are also defined in the Schedule 1 - Dictionary.

specified condition means one of the following:
(a) adrenal neoplasm;
(b) adrenocorticotropic hormone (ACTH) secreting neoplasm of the pituitary gland;
(c) macronodular adrenal hyperplasia;
(d) micronodular adrenal hyperplasia; or
(e) neuroendocrine neoplasm.

Note: adrenal neoplasm and neuroendocrine neoplasm are also defined in the Schedule 1 - Dictionary.

specified list of drugs means:
(a) amprenavir;
(b) atazanavir;
(c) boceprevir;
(d) clarithromycin;
(e) darunavir;
Schedule 1 - Dictionary

(f) delavirdine;
(g) erythromycin;
(h) fosamprenavir;
(i) indinavir;
(j) isoniazid;
(k) itraconazole;
(l) ketoconazole;
(m) lopinavir;
(n) nelfinavir;
(o) posaconazole;
(p) ritonavir;
(q) saquinavir;
(r) telaprevir;
(s) telithromycin;
(t) tipranavir; or
(u) voriconazole.

**terminal event** means the proximate or ultimate cause of death and includes the following:

(a) pneumonia;
(b) respiratory failure;
(c) cardiac arrest;
(d) circulatory failure; or
(e) cessation of brain function.

**VEA** means the *Veterans’ Entitlements Act 1986*. 