



Australian Government
Repatriation Medical Authority

Statement of Principles
concerning
ADRENAL INSUFFICIENCY
(Reasonable Hypothesis)
(No. 71 of 2018)

The Repatriation Medical Authority determines the following Statement of Principles under subsection 196B(2) of the *Veterans' Entitlements Act 1986*.

Dated 24 August 2018

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

A handwritten signature in black ink, appearing to read 'N. Saunders'.

Professor Nicholas Saunders AO
Chairperson

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1 Name

This is the Statement of Principles concerning *adrenal insufficiency (Reasonable Hypothesis)* (No. 71 of 2018).

2 Commencement

This instrument commences on 24 September 2018.

3 Authority

This instrument is made under subsection 196B(2) of the *Veterans' Entitlements Act 1986*.

4 Repeal

The Statement of Principles concerning adrenal insufficiency No. 74 of 2009 (Federal Register of Legislation No. F2009L04045) made under subsection 196B(2) of the VEA is repealed.

5 Application

This instrument applies to a claim to which section 120A of the VEA or section 338 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 adrenal insufficiency and death from adrenal insufficiency.

*Meaning of **adrenal insufficiency***

- (2) For the purposes of this Statement of Principles, adrenal insufficiency:
- (a) means an endocrine disease characterised by biochemically-demonstrated deficient production of adrenal cortical hormones, sufficient to produce clinical symptoms and signs, and to necessitate glucocorticoid, mineralocorticoid or adrenal androgen replacement therapy; and
 - (b) includes drug-induced adrenal insufficiency; and
 - (c) excludes heritable and congenital forms of adrenal insufficiency.

Note 1: Adrenal cortical hormones are mineralocorticoids, cortisol and adrenal androgens.

Note 2: Clinical symptoms and signs of adrenal insufficiency are nonspecific and may include nausea, vomiting, abdominal cramps and diarrhoea, fatigue, myalgias, arthralgias, weakness, fever, dizziness, weight loss, amenorrhoea, decreased libido and depression.

Note 3: Adrenal insufficiency may be acute or chronic. Acute adrenal insufficiency may present as an adrenal crisis. Primary adrenal insufficiency is also known as Addison disease.

- (3) While adrenal insufficiency attracts ICD-10-AM code E27.1, E27.2, E27.3, E27.4, E89.6, A18.7 or A39.1, in applying this Statement of Principles the meaning of adrenal insufficiency 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 Problems, Tenth Revision, Australian Modification (ICD-10-AM)*, Tenth Edition, effective date of 1 July 2017, copyrighted by the Independent Hospital Pricing Authority, ISBN 978-1-76007-296-4.

Death from adrenal insufficiency

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

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

8 Basis for determining the factors

The Repatriation Medical Authority is of the view that there is sound medical-scientific evidence that indicates that adrenal insufficiency and death from adrenal insufficiency can be related to relevant service rendered by veterans, members of Peacekeeping Forces, 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 as a minimum exist before it can be said that a reasonable hypothesis has been raised connecting adrenal insufficiency or death from adrenal insufficiency with the circumstances of a person's relevant service:

- (1) having an autoimmune disorder involving the adrenal glands at the time of the clinical onset of adrenal insufficiency;
- (2) having infiltration of the adrenal glands due to a disorder from the specified list of infiltrative disorders at the time of the clinical onset of adrenal insufficiency;

Note: *specified list of infiltrative disorders* is defined in the Schedule 1 - Dictionary.

- (3) having infection with human immunodeficiency virus before the clinical onset of adrenal insufficiency;

- (4) having an injury or surgery to:
- (a) both adrenal glands, or
 - (b) a single adrenal gland:
 - (i) where there is only one functional adrenal gland; or
 - (ii) as surgical treatment for Cushing syndrome;

within the one year before the clinical onset of adrenal insufficiency;

- (5) having haemorrhage or infarction of:
- (a) both adrenal glands, or
 - (b) a single functional adrenal gland, where there is only one functional adrenal gland;

within the one year before the clinical onset of adrenal insufficiency;

Note: Common causes of adrenal haemorrhage or infarction include trauma to the adrenal gland, heparin-induced thrombocytopenia, anticoagulant therapy, antiphospholipid syndrome, sepsis, malignancy and haematological disorder.

- (6) having an infection of the adrenal glands with an organism from the specified list of infectious organisms at the time of the clinical onset of adrenal insufficiency;

Note: *specified list of infectious organisms* is defined in the Schedule 1 - Dictionary.

- (7) being treated with a drug or a drug from a class of drugs from Specified List 1 of drugs within the three months before the clinical onset of adrenal insufficiency;

Note: *Specified List 1 of drugs* is defined in the Schedule 1 - Dictionary.

- (8) having glucocorticoid therapy as specified, before the clinical onset of adrenal insufficiency, and where the glucocorticoid therapy as specified has ceased or decreased, the last dose of the therapy was received within the one year before the clinical onset of adrenal insufficiency;

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

- (9) being treated with medroxyprogesterone acetate or megestrol acetate for a malignant disease or human immunodeficiency virus infection:
- (a) for a continuous period of at least four weeks before the clinical onset of adrenal insufficiency; and
 - (b) where such treatment has ceased, the last dose was received within the three months before the clinical onset of adrenal insufficiency;

- (10) having hypopituitarism with adrenocorticotrophic hormone deficiency, at the time of the clinical onset of adrenal insufficiency;

- (11) having a critical illness or injury within the one year before the clinical onset of adrenal insufficiency;

Note: *critical illness or injury* is defined in the Schedule 1 - Dictionary.

- (12) for adrenal crisis only, having an acute, severe stressor within the seven days before the clinical onset of adrenal insufficiency;

Note: *acute, severe stressor* and *adrenal crisis* are defined in the Schedule 1 - Dictionary.

- (13) having an autoimmune disorder involving the adrenal glands at the time of the clinical worsening of adrenal insufficiency;

- (14) having infiltration of the adrenal glands due to a disorder from the specified list of infiltrative disorders at the time of the clinical worsening of adrenal insufficiency;

Note: *specified list of infiltrative disorders* is defined in the Schedule 1 - Dictionary.

- (15) having infection with human immunodeficiency virus before the clinical worsening of adrenal insufficiency;

- (16) having an injury or surgery to:

- (a) both adrenal glands, or
(b) a single adrenal gland:

- (i) where there is only one functional adrenal gland; or
(ii) as surgical treatment for Cushing syndrome;

within the one year before the clinical worsening of adrenal insufficiency;

- (17) having haemorrhage or infarction of:

- (a) both adrenal glands, or
(b) a single functional adrenal gland, where there is only one functional adrenal gland;

within the one year before the clinical worsening of adrenal insufficiency;

Note: Common causes of adrenal haemorrhage or infarction include trauma to the adrenal gland, heparin-induced thrombocytopenia, anticoagulant therapy, antiphospholipid syndrome, sepsis, malignancy and haematological disorder.

- (18) having an infection of the adrenal glands with an organism from the specified list of infectious organisms at the time of the clinical worsening of adrenal insufficiency;

Note: *specified list of infectious organisms* is defined in the Schedule 1 - Dictionary.

- (19) being treated with a drug or a drug from a class of drugs from Specified List 1 of drugs within the three months before the clinical worsening of adrenal insufficiency;

Note: *Specified List 1 of drugs* is defined in the Schedule 1 - Dictionary.

- (20) having glucocorticoid therapy as specified, before the clinical worsening of adrenal insufficiency:
- (a) where the glucocorticoid therapy as specified is not being taken for the treatment of adrenal insufficiency; and
 - (b) where the glucocorticoid therapy as specified has ceased or decreased, the last dose of the therapy was received within the one year before the clinical worsening of adrenal insufficiency;

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

- (21) being treated with medroxyprogesterone acetate or megestrol acetate for a malignant disease or human immunodeficiency virus infection:
- (a) for a continuous period of at least four weeks before the clinical worsening of adrenal insufficiency; and
 - (b) where such treatment has ceased, the last dose was received within the three months before the clinical worsening of adrenal insufficiency;

- (22) having hypopituitarism with adrenocorticotrophic hormone deficiency, at the time of the clinical worsening of adrenal insufficiency;

- (23) having a critical illness or injury within the one year before the clinical worsening of adrenal insufficiency;

Note: *critical illness or injury* is defined in the Schedule 1 - Dictionary.

- (24) for adrenal crisis only, having an acute, severe stressor within the seven days before the clinical worsening of adrenal insufficiency;

Note: *acute, severe stressor* and *adrenal crisis* are defined in the Schedule 1 - Dictionary.

- (25) inability to obtain appropriate clinical management for adrenal insufficiency.

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 factors set out in subsections 9(13) to 9(25) apply only to material contribution to, or aggravation of, adrenal insufficiency where the person's adrenal insufficiency 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(2) 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:

acute, severe stressor means a physical or psychological stimulus or event that causes a sudden, intense psychological or physical response.

Note: Examples of acute, severe stressors include:

- (a) abrupt cessation or lowering of glucocorticoid therapy;
- (b) acute hepatic failure;
- (c) alcohol intoxication;
- (d) atrial fibrillation;
- (e) being exposed to an environment of extreme heat during a heatwave;
- (f) critical illness or injury;
- (g) dehydration;
- (h) experiencing a category 1A stressor;
- (i) experiencing an acute, severe, emotional stressor;
- (j) febrile illness;
- (k) gastrointestinal infection;
- (l) long distance flight;
- (m) migraine;
- (n) oesophageal variceal bleeding;
- (o) physical trauma or injury;
- (p) serious acute illness;
- (q) surgery;
- (r) thyrotoxicosis;
- (s) undertaking physical activity of five METs or more; and
- (t) wasp or bee sting.

Note: ***category 1A stressor, critical illness or injury, extreme heat*** and ***MET*** are also defined in the Schedule 1 – Dictionary.

adrenal crisis means a constellation of symptoms that indicate severe adrenal insufficiency of rapid onset causing acute haemodynamic decompensation. Characteristic symptoms and signs are hypotension, tachycardia, hypovolaemia (shock), lethargy, hypoglycaemia, disorientation, impaired consciousness, seizures and coma.

Note 1: Adrenal crisis is a medical emergency that requires treatment with injectable hydrocortisone and fluid support. Adrenal crisis is also known as an Addisonian crisis.

Note 2: Adrenal crisis may be the first presentation of undiagnosed adrenal insufficiency, or may complicate existing chronic adrenal insufficiency.

adrenal insufficiency—see subsection 7(2).

category 1A stressor means one of the following severe traumatic events:

- (a) experiencing a life-threatening event;
- (b) being subject to a serious physical attack or assault including rape and sexual molestation; or
- (c) being threatened with a weapon, being held captive, being kidnapped or being tortured.

critical illness or injury means any physical injury or illness requiring mechanical ventilation support or admission to an intensive care unit, or which causes septicaemia, adult respiratory distress syndrome, acute renal tubular necrosis, disseminated intravascular coagulation or multiple organ failure.

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:

Glucocorticoid	Minimum cumulative dose (milligrams)	Minimum average rate (milligrams/day)
betamethasone	18	0.6
cortisone	750	25
dexamethasone	22	0.7
methylprednisolone	120	4
paramethasone	60	2
prednisolone	150	5
prednisone	150	5
triamcinolone	120	4

equivalent inhaled glucocorticoid means:

- (a) 800 micrograms of beclometasone;
- (b) 640 micrograms of ciclesonide;
- (c) 400 micrograms of fluticasone furoate;
- (d) 1 000 micrograms of fluticasone propionate;
- (e) 4 000 micrograms of triamcinolone; or
- (f) a therapeutically equivalent dose of another inhaled glucocorticoid.

extreme heat means 40 degrees Celsius or above.

glucocorticoid therapy as specified means:

- (a) applying a high or very high potency topical glucocorticoid to at least 10% of total skin surface area, daily, for a continuous period of at least three months; or
- (b) inhaling at least 1 600 micrograms of budesonide, or equivalent inhaled glucocorticoid, daily, for a continuous period of at least three months; or
- (c) taking:
 - (i) hydrocortisone, orally or by injection:
 - (A) to a cumulative dose of at least 600 milligrams; and
 - (B) at a minimum dose rate averaging 20 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 four 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 Specified List 2 of drugs, daily, for a continuous period of at least four weeks; or

- (f) using an ocular glucocorticoid, daily, for a continuous period of at least six months; or
- (g) using an intranasal glucocorticoid, at an average daily dose exceeding 400 micrograms of betamethasone 0.1%, or equivalent intranasal glucocorticoid, for a continuous period of at least six months; or
- (h) using glucocorticoid containing enemas, daily, for a continuous period of at least six months; or
- (i) taking any glucocorticoid therapy that causes Cushing syndrome.

Note: *equivalent glucocorticoid therapy*, *equivalent inhaled glucocorticoid*, *high or very high potency topical glucocorticoid* and *Specified List 2 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.

iron overload means an accumulation of excess iron in tissues and organs which has been confirmed by elevated ferritin or transferrin saturation levels. Causes include haemochromatosis or blood transfusions.

MET means a unit of measurement of the level of physical exertion. 1 MET = 3.5 ml of oxygen/kg of body weight per minute, 1.0 kcal/kg of body weight per hour or resting metabolic rate.

MRCA means the *Military Rehabilitation and Compensation Act 2004*.

relevant service means:

- (a) operational service under the VEA;
- (b) peacekeeping service under the VEA;
- (c) hazardous service under the VEA;
- (d) British nuclear test defence service under the VEA;
- (e) warlike service under the MRCA; or
- (f) non-warlike service under the MRCA.

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

Specified List 1 of drugs means:

- (a) aminoglutethimide;
- (b) imidazole antifungals;
- (c) busulfan;
- (d) chlorpromazine;
- (e) etomidate;
- (f) imipramine;
- (g) immune checkpoint inhibitors;
- (h) metyrapone;

- (i) mifepristone;
- (j) mitotane;
- (k) rifampicin;
- (l) suramin; or
- (m) treosulfan.

Specified List 2 of drugs means:

- (a) amprenavir;
- (b) atazanavir;
- (c) clarithromycin;
- (d) darunavir;
- (e) delavirdine;
- (f) diltiazem;
- (g) erythromycin;
- (h) fluconazole;
- (i) fosamprenavir;
- (j) indinavir;
- (k) itraconazole;
- (l) ketoconazole;
- (m) lopinavir;
- (n) nelfinavir;
- (o) posaconazole;
- (p) ritonavir;
- (q) saquinavir;
- (r) telithromycin;
- (s) tipranavir;
- (t) verapamil; or
- (u) voriconazole.

specified list of infectious organisms means:

- (a) *Blastomyces dermatitidis*;
- (b) *Coccidioides immitis*;
- (c) *Coccidioides posadasii*;
- (d) *Cryptococcus neoformans*;
- (e) cytomegalovirus;
- (f) *Echinococcus granulosus*;
- (g) herpes simplex virus;
- (h) *Histoplasma capsulatum*;
- (i) *Mycobacterium avium-intracellulare*;
- (j) *Mycobacterium kansasii*;
- (k) *Mycobacterium tuberculosis*;
- (l) *Nocardia spp*;
- (m) *Paracoccidioides brasiliensis*;
- (n) *Pneumocystis carinii*; or
- (o) *Toxoplasmosis gondii*.

specified list of infiltrative disorders means:

- (a) a primary or metastatic neoplasm;
- (b) amyloidosis;

- (c) iron overload; or
- (d) sarcoidosis.

Note: *iron overload* is also defined in the Schedule 1 - Dictionary.

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*.