

Table 17: Clinical evidence profile: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h) for secondary and tertiary adrenal insufficiency [SF-36 Outcomes]

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With comparator	With intervention		Risk with comparator	Risk difference with intervention
SF36 - Physical functioning - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Physical functioning - A vs B was 79.5 points	MD 9 points higher (9.74 lower to 27.74 higher)
SF36 - Physical functioning - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Physical functioning - A vs C was 80.5 points	MD 8 points higher (10.99 lower to 26.99 higher)
SF36 - Physical functioning - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Physical functioning - B vs C was 80.5 points	MD 1 points lower (22.26 lower to 20.26 higher)
SF36 - Role Physical - A vs B (follow-up: 6 weeks)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Role Physical - A vs B was 62.5 points	MD 15 points higher (17.36 lower to 47.36 higher)
SF36 - Role Physical - A vs C (follow-up: 6 weeks)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Role Physical - A vs C was 55 points	MD 22.5 points higher (14.15 lower to 59.15 higher)
SF36 - Role Physical - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Role Physical - B vs C was 55 points	MD 7.5 points higher (28.29 lower to 43.29 higher)
SF36 - Bodily pain - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Bodily pain - A vs B was 82.5 points	MD 2.6 points higher (16.67 lower to 21.87 higher)
SF36 - Bodily pain - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Bodily pain - A vs C was 76.5 points	MD 8.6 points higher (10.2 lower to 27.4 higher)
SF36 - Bodily pain - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Bodily pain - B vs C was 76.5 points	MD 6 points higher (14.43 lower to 26.43 higher)
SF36 - General health - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^d	none	⊕○○○ Very low	10	10	-	The mean SF36 - General health - A vs B was 61.8 points	MD 1 points higher (13.06 lower to 15.06 higher)
SF36 - General health - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^d	none	⊕○○○ Very low	10	10	-	The mean SF36 - General health - A vs C was 59.8 points	MD 3 points higher (11.81 lower to 17.81 higher)
SF36 - General health - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^d	none	⊕○○○ Very low	10	10	-	The mean SF36 - General health - B vs C was 59.8 points	MD 2 points higher (10.3 lower to 14.3 higher)
SF36 - Vitality - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^d	none	⊕○○○ Very low	10	10	-	The mean SF36 - Vitality - A vs B was 47.5 points	MD 15 points higher (6.14 lower to 36.14 higher)
SF36 - Vitality - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^d	none	⊕○○○ Very low	10	10	-	The mean SF36 - Vitality - A vs C was 44 points	MD 18.5 points higher (3.15 lower to 40.15 higher)
SF36 - Vitality - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^d	none	⊕○○○ Very low	10	10	-	The mean SF36 - Vitality - B vs C was 44 points	MD 3.5 points higher (17.46 lower to 24.46 higher)
SF36 - Social functioning - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Social functioning - A vs B was 92.5 points	MD 2.5 points lower (16.11 lower to 11.11 higher)
SF36 - Social functioning - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Social functioning - A vs C was 85 points	MD 7.5 points higher (6.61 lower to 21.61 higher)
SF36 - Social functioning - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Social functioning - B vs C was 85 points	MD 7.5 points higher (6.61 lower to 21.61 higher)
SF36 - Role emotional - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^e	none	⊕○○○ Very low	10	10	-	The mean SF36 - Role emotional - A vs B was 66.6 points	MD 16.7 points higher (17.35 lower to 50.75 higher)
SF36 - Role emotional - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^e	none	⊕○○○ Very low	10	10	-	The mean SF36 - Role emotional - A vs C was 73.3 points	MD 10 points higher (23.77 lower to 43.77 higher)
SF36 - Role emotional - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^e	none	⊕○○○ Very low	10	10	-	The mean SF36 - Role emotional - B vs C was 73.3 points	MD 6.7 points lower (42.81 lower to 29.41 higher)
SF36 - Mental health - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Mental health - A vs B was 80 points	MD 0.4 points lower (16.49 lower to 15.69 higher)
SF36 - Mental health - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Mental health - A vs C was 80 points	MD 0.4 points lower (15.83 lower to 15.03 higher)
SF36 - Mental health - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious ^a	not serious	serious ^b	very serious ^c	none	⊕○○○ Very low	10	10	-	The mean SF36 - Mental health - B vs C was 80 points	MD 0 points (15.92 lower to 15.92 higher)

Explanations

- a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias.
- b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]
- c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3)
- d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)
- e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		

NHP - Energy level - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^c	none	10	10	-	MD 1.2 points higher (36.54 lower to 38.94 higher)	⊕○○○ Very low	
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NHP - Energy level - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^d	none	10	10	-	MD 5 points lower (40.56 lower to 30.56 higher)	⊕○○○ Very low	
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Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		

NHP - Energy level - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^d	none	10	10	-	MD 6.2 points lower (41.25 lower to 28.85 higher)	⊕○○○ Very low	
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NHP - Pain - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^e	none	10	10	-	MD 1.1 points higher (15.72 lower to 17.92 higher)	⊕○○○ Very low	
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NHP - Pain - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^f	none	10	10	-	MD 2.5 points lower (21.7 lower to 16.7 higher)	⊕○○○ Very low	
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NHP - Pain - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^f	none	10	10	-	MD 3.6 points lower (20.11 lower to 12.91 higher)	⊕○○○ Very low	
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NHP - Emotional reaction - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^g	none	10	10	-	MD 1.2 points higher (10.33 lower to 12.73 higher)	⊕○○○ Very low	
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NHP - Emotional reaction - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^b	none	10	10	-	MD 0.1 points lower (12.47 lower to 12.27 higher)	⊕○○○ Very low	

NHP - Emotional reaction - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^b	none	10	10	-	MD 1.3 points lower (15.6 lower to 13 higher)	⊕○○○ Very low	
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NHP - Sleep - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^c	none	10	10	-	MD 5.4 points higher (18.3 lower to 29.1 higher)	⊕○○○ Very low	
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NHP - Sleep - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	serious ^d	none	10	10	-	MD 9.8 points higher (8.29 lower to 27.89 higher)	⊕○○○ Very low	
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NHP - Sleep - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^e	none	10	10	-	MD 4.4 points higher (17.4 lower to 26.2 higher)	⊕○○○ Very low	
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NHP - Social isolation - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^c	none	10	10	-	MD 1 points higher (14.2 lower to 16.2 higher)	⊕○○○ Very low	
NHP - Social isolation - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious ^a	not serious	serious ^b	extremely serious ^m	none	10	10	-	MD 0 points (0 to 0)	⊕○○○ Very low	
NHP - Social isolation - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious ^a	not serious	serious ^b	extremely serious ^m	none	10	10	-	MD 0 points (0 to 0)	⊕○○○ Very low	
NHP - Physical abilities - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious ^a	not serious	serious ^b	very serious ⁿ	none	10	10	-	MD 4.2 points lower (20.78 lower to 12.38 higher)	⊕○○○ Very low	
NHP - Physical abilities - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^o	none	10	10	-	MD 5.5 points lower (21.43 lower to 10.43 higher)	⊕○○○ Very low	
NHP - Physical abilities - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious ^a	not serious	serious ^b	very serious ^o	none	10	10	-	MD 1.3 points lower (19.85 lower to 17.25 higher)	⊕○○○ Very low	

- a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias. Study authors also do not provide details around blinding so outcomes are at risk of measurement bias.
- b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]
- c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 21.25)
- d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 18.65)
- e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.8)
- f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.8)
- g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.75)
- h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 8.55)
- i. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 15.2)
- j. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 8.85)
- k. Downgraded by 1 increment as confidence interval crossed both MIDs (+/- 8.85)
- l. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.65)
- m. Downgraded by 2 increments because comparator value was not captured
- n. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.9)
- o. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.25)