New Medicine Assessment

Testosterone (Testim®) for female sexual dysfunction post oophorectomy or primary ovarian failure

Recommendation: BLACK

Testosterone gel (Testim®) is **not** recommended for female sexual dysfunction post oophorectomy or primary ovarian failure.

The evidence to support the use of testosterone **gel** is limited to a single trial in 53 women and is only in patients with intact ovaries with female sexual dysfunction.

There are currently no published trials on the use of testosterone **gel** in women with FSD post oophorectomy.

There are several trials assessing the effectiveness of testosterone patches, these are now discontinued, however, when they were available they were not recommended for use due to questions around clinical significance of improvement (despite being statistical significance) compared to placebo.

Summary of supporting evidence:

- The majority of the evidence available supporting the use of transdermal testosterone relates to testosterone patches.
- The sizes of the populations in which testosterone gel was assessed for effectiveness were small and the results were based on subjective outcomes.
- It is questionable whether the median increase in score of 1 point (out of 7) is clinically significant despite being statistically significant compared to placebo.
- The evidence for the testosterone patches shows a modest improvement in HSDD.
- It is not clear what testosterone level needs to be attained to improve the symptoms of HSDD and it has been found that the serum levels do not always correspond to the symptoms are exhibited. It is believed that psychosocial support will provide the best outcomes for patients with female sexual dysfunction and HSDD.
- The proposed preparation is an off-label use of a licensed drug, which is formulated for men who require higher doses. Therefore, there are concerns over the ability to administer doses for the female population as they require significantly lower doses.
- Due to the inability to measure accurately the small doses required there is a potential for the patient to administer higher doses than that required and could leave patients at risk of supraphysiologic testosterone levels, which can lead to irreversible adverse events e.g. clitoral enlargement and voice changes.

- There are a number of concerns over the safety of transdermal testosterone. Some of the data published is contradictory but caution is still advised by regulatory bodies. Evidence suggests that the possible safety issues are dose related. This supports concerns relating to the inability to accurately measure doses using the proposed preparation.
- The cost of testosterone gel is relatively inexpensive as a tube is expected to last 10 days. Approximate annual costs would be £39.

Details of Review

Name of medicine (generic & brand name)**:**

Testosterone (Testim®)[1]

Strength(s) and form(s):

50 mg/5 g gel[1]

Dose and administration:

The dose recommended by clinicians is 1/10th of a 5 g gel tube, but could be from 1/4 to 1/20th of a tube. The requesting clinician states that the patient using the product would need to estimate the 1/10th (i.e. make the tube last 10 days).

BNF therapeutic class / mode of action

6.4.2 Male sex hormones and antagonists[1]

Licensed indication(s):

Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.[1]

Proposed use (if different from, or in addition to, licensed indication, or use is unlicensed):

The requested indication is for female sexual dysfunction post oophorectomy or primary ovarian failure. This use is an unlicensed indication.

Course and unit cost:

Testosterone (Testim) 1% gel, 30 x 5 g tubes = £32.00 (MIMS March 2015).[2]

Based on 1/10th of a tube (see above) the cost would be approx. £3 per month (£39/year).

Current standard of care/comparator therapies:

The current recommended therapy is tibilone, unopposed oestrogen and testosterone implant. The testosterone gel is to replace the implant, when patients have tried both unopposed oestrogen HRT and tibilone. If there has been no improvement in female sexual dysfunction it will be used in addition to oestrogen HRT. (from application form)

Relevant NICE guidance:

There is no relevant NICE that exists for managing female sexual dysfunction post oophorectomy or primary ovarian failure. There are recently reviewed Clinical Practice Guidelines “Androgen therapy in Women”[3]

Reason for review

A request was received from East Lancashire Hospitals NHS Trust to change from testosterone implant to topical testosterone gel as a third line therapy for female sexual dysfunction.

Background and context

Female sexual dysfunction (FSD) can occur at any age but is most common around middle age. Two important overlapping factors that affect female sexuality are the aging process and the menopause.[4] The decrease in oestrogen associated with the menopause leads to epithelial thinning as well as reduced vasocongestion and lubrication during sexual arousal which leads to dryness and dyspareunia (pain during or after intercourse).[4] Some of the manifestations of menopause; decreased libido, fatigue and decreased sexual activity, can be attributed to the decline in testosterone levels that begins in a womans twenties. Levels can drop by 50% by the age of 45.[4] There is a consensus that FSD is multifactorial, with mental health and interpersonal factors contributing. FSD usually involves diminished sexual motivation/interest, minimal desire for sex, reduced arousal and orgasmic response, with/without sexual pain.[4]

Hypoactive Sexual Desire Disorder (HSDD) is a subset of FSD and has been defined as a persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity causing personal distress.[4,5] The diagnosis has to be made clinically, and questionnaires are used to assess treatment response.[4] There can be many causes of HSDD, usually the underlying cause is the age related decline in menopausal endocrinology, but other factors need to be considered including; unhappy life event, psychosocial dysfunctions, depression, drugs, medical gynaecological disorders, natural and iatrogenic disruptions to androgen production.[4] A European study reported the prevalence to be; 7% in younger premenopausal women, 16% in younger surgically menopausal women, with figures for older naturally and surgically menopausal women lying in between (9% and 12% respectively).[4]

It is recommended that psychosocial interventions, including basic counselling, physiotherapy and psychosexual interventions form basis of the management of HSDD. Pharmacological therapies, if required, can include; treatment with oestrogens, combined oestrogen and testosterone, tibilone and dihydroepiandrotestosterone (DHEA). It is suggested that a number of drugs including antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) can contribute to HSDD and it is recommended that they are reviewed with a view to discontinuing or reducing the dose. Oral oestrogens, used for menopausal replacement, can impair the effect of testosterone. There seems to be improvement in HSDD when chronic diseases are effectively managed e.g. HTN, diabetes.[4,6]

In addition to declining oestrogen secretion in peri- and post-menopausal years there is also a decline in androgen levels. There appears to be evidence that testosterone replacement therapy, given to postmenopausal women reporting low sexual desire, may improve desire, subjective arousal, vaginal blood flow and increased frequency of orgasm. Testosterone interacts with the receptors in the hypothalamus which activates the dopaminergic pathway that modulates the seeking-appetite-lust system. It is unclear what testosterone level can identify women with diminished sexual function and in fact studies have shown that there were no differences in serum testosterone levels between women experiencing HSDD and those who are not. It is advised that if testosterone therapy is to be tried that the transdermal route is preferred for depleted androgen as opposed to oral therapy.[4,7]

The Endocrine Society Clinical Practice Guideline recommends, for those women with HSDD, a 3 to 6 months trial of testosterone, for those who are properly diagnosed and in whom therapy is not contraindicated. Baseline levels should be measured and after 3 to 6 weeks. If there is no response after 6 months of therapy treatment should be discontinued. If therapy is continued testosterone levels should be measured every 6 months to monitor excessive use and signs of androgen excess. There is no safety and efficacy data for testosterone therapy after 24 months. It is important to note that these recommendations are derived from evidence from transdermal testosterone patches.[3]

Summary of evidence

Summary of efficacy data in proposed use:

There is limited evidence to support the use of topical testosterone gel in HSDD. A small double blind crossover RCT (n=60) assessed the efficacy of testosterone 10 mg gel applied topically in post-menopausal women. Patients had to have preserved ovaries, serum testosterone levels < 2.0 mmol/L and total or significant loss of libido during the post-menopausal period. 30 patients were treated with testosterone gel for 3 months and crossed over to placebo for 3 months; the remaining 30 patients were treated with placebo for the first 3 months and then crossed over to testosterone gel for 3 months. 53 women completed the study and were included in the statistical analysis.[8]

Efficacy was assessed with a variation of the "McCoy questionnaire" (designed to assess aspects of female sexuality) and the quality of life was assessed using a psychological general well-being questionnaire. The paper reports the median values for individual items in the McCoy questionnaire (with a range of values from 1 to 7). For the sub-question "frequency of sexual activity" the baseline (before treatment) median value was 2, the median value for the placebo period of treatment was 3 and for the testosterone gel treatment phase was 4. The paper reported that for all patients (i.e. both groups from the crossover period) $p < 0.0001$. For the question "sexual thoughts/fantasies" the baseline score was 2, during the placebo treatment phase the median score was 2 and for the testosterone treatment the score was 3. The paper reports a $p<0.0001$ when pooling the results of both groups. For "satisfaction with orgasms" the baseline median value was 5, whilst treated with placebo was 5 and whilst treated with testosterone was also 5. The paper reports the $p=0.012$ when pooling the results from both groups.[8]

For the QOL questionnaire, anxiety was scored as 23 at baseline, 24 for the placebo phase and 27 for the testosterone treatment phase, $p<0.001$. For the measure of depressed mood the baseline score was 16 and during the placebo period this was reported as 15 and for the testosterone period 16 ($p=0.382$). For positive well-being the baseline score was 15 during the placebo treatment phase the score was 16 and for the testosterone treatment phase this was reported as 17 ($p=0.010$).[8]

Other efficacy data:

No other trials were found for assessing the efficacy of testosterone **gel** in the treatment of HSDD. However, there were trials found that assessed the efficacy of testosterone **cream** in patients with HSDD, one of these was in pre-menopausal women and therefore not reviewed as not in the population being proposed.[9]

Another RCT (n=36) assessed the safety and efficacy of 10 mg topical testosterone **cream** for low sexual desire in postmenopausal hysterectomised women who were already on transdermal oestrogen. The study was a randomized, placebo-controlled, cross-over study (each period being of 3 months' duration) in menopausal women who were not depressed, were in a stable relationship and who fulfilled diagnostic criteria for low sexual desire, as measured by the Brief Index of Sexual Function for Women (BISF-W). The primary outcome measure was improvement in the sexuality score as measured by a validated tool (BISF-W); secondary measures were sub-scores of the BISF-W, effect on mood and energy, lipids and testosterone levels. It was found that testosterone cream significantly improved sexual desire, frequency of sex, receptivity and initiation as measured by the BISF-W score. It did not change mood, energy, lipids, blood pressure or weight over the study period. (This information was obtained from the abstract – the full paper was unobtainable).[10]

A phase III randomised crossover trial (n=150) assessed the efficacy of testosterone 2 % **cream** in women who had a history of cancer who were bothered by a decrease in their libido. Subjects had to be post-menopausal and have a score of < 8 (on a scale of 0-10, 10 being highest interest) for sexual desire. They were randomised to 10.4 mg testosterone cream (measured using 1/8 of a teaspoon) or placebo for 4 weeks and then crossed over for a further 4 weeks of treatment with the opposite treatment. The primary endpoint, measured by self-reported questionnaires, at 0, 4 and 8 weeks, measured sexual desire. The changes in sexual functioning questionnaire asked three questions about desire and interest and two questions about desire and frequency on a 5 point scale.

The results showed that for the primary outcome, libido, there was no statistically significant difference in the combined desire subscales between either groups for both the first and second four weeks of treatment. The same was also true for the combined scores for the pleasure subscale; no statistically significant difference between the testosterone and placebo treatment groups in either the first or second four weeks of treatment. The mean baseline serum free testosterone levels reported were 0.5 ng/dL (normal range 0.3 to 1.9 ng/dL). These levels statistically significantly increased after 4 weeks of treatment with testosterone (in both treatment periods); mean 1.63 ng/dL (CI 1.24 to 2.02) for the first 4 weeks (placebo 0.18 (CI -0.11 to 0.47) and for the second 4 weeks the mean was 1.51 ng/dL (CI 1.11 to 1.91) for those on testosterone and 0.08 (CI -0.11 to 0.27) for those on placebo. Therefore the increase in testosterone levels did not confer improvements in sexual desire.[11]

It is important to note that there are several trials assessing the efficacy of testosterone patches in HSDD or FSD. However, no patches are currently licensed in the UK. The Scottish Medicines Consortium reviewed two key papers for the use of testosterone patches (300 micrograms/24 hours transdermal patch) and advised that they were not recommended for use in HSDD in bilaterally oophorectomised (surgically induced menopause) women receiving concomitant oestrogen therapy. They stated that the manufacturer did not present sufficiently robust economic analysis to gain acceptance. The review of the two RTCs revealed a statistically significant improvement in the number of satisfying sexual episodes per 4 week period for those treated with the patch compared to placebo. SMC highlighted a number of issues with the trials; the studies excluded women who may be eligible for treatment and therefore the trial population may have not been representative of women who would be prescribed transdermal testosterone. It was noted that there was a large placebo response in both trials. There were questions raised as to the clinical relevance of the effect size; increase in one satisfactory episode per 4 week period, an increase in sexual desire disorder of 6-7 points on a 100-point scale and a decrease in personal distress of 7 points again on a 100 point scale.[12]

Midlands Therapeutic Review and Advisory Committee (MTRAC) also reviewed four double blind RCTs assessing testosterone 300µg/day patches in women who had undergone surgically-induced menopause and were receiving a stable dose of oestrogen, and expressed concern about their loss of libido, one study also evaluated patches delivering 150µg and 450µg of testosterone per day. MTRAC concluded “The testosterone patch is not considered suitable for prescribing. Current clinical evidence for efficacy is weak, based on short-term (24 week) trials using subjective outcomes. The size of benefit found was small, with questionable clinical relevance and a large placebo effect. There is concern about the potential harmful effects of long-term use on breast tissue and the cardiovascular system (and endometrium if used outside the product license).”[13]

There a number of testosterone gels, for topical use in FSD, in development but no information is available on their plans to file for licensing in the UK. Some of the trials did not meet co-primary or secondary endpoints and further trials are on-going – see entries on www.ukmi.nhs.uk for further up to date information.

Summary of safety data:

Theoretically patients whose testosterone level is brought to and maintained at the "normal" physiological range should not experience AEs whilst on testosterone therapy. However, it is difficult not to exceed the ideal range, as there is no specific recommended dose and depends on the individual patient being treated. Also the preparation that is proposed to be used is not designed to measure the dose of testosterone that is suggested for women as it is licensed for men, who require much higher doses. The dose administered can be extremely variable, the proposal is for 1/10th of a 5 g tube (which will be difficult to measure accurately), this is of concern given that previous studies have demonstrated a fine line between lack of efficacy doses and doses that can lead to unwanted androgenergic AEs. Once testosterone levels become supraphysiologic it can cause masculinization (acne, hirsutism, deepening of the voice, and androgenic alopecia), some of these, e.g. clitoral enlargement and voice changes, can be irreversible.

The primary trial assessing the effectiveness of testosterone gel grouped the adverse events (AEs) into two categories; influence on mood (headache, weight, appetite) was reported in 7 patients in the placebo treatment phase and 6 patients in the testosterone treatment phase; skin related (acne, facial hair, hair on legs) was reported in 9 patients during placebo therapy and 11 patients during testosterone treatment. It should be noted that the mean testosterone serum levels increased more than 10-fold during the testosterone treatment phase (after 3 months of treatment) to 7.8 +/-5.2 nmol/L (which exceeds what is classed as the normal range 0.22 – 2.9 nmol/L).[8]

There have been concerns raised that transdermal testosterone in physiologic to slightly supraphysiologic doses is effective but that the degree of increased sexual desire above placebo is not enough to justify potential long-term complications. [5,14]

There are a number of concerns over the safety of testosterone these include, breast cancer and endometrial cancer risk and cardiovascular safety.

Breast cancer - a prospective case control study found there was an association between testosterone therapy and breast cancer risk, although estrodiol levels were not taken into account in the analysis. Other recent studies have not shown a significant association between breast cancer risk and testosterone. No RCTs have been adequately powered to detect an increase in breast cancer risk.[5,14] The relationship between testosterone and breast cancer remains unclear. [5]

Endometrial cancer - A paper has confirmed that when adjusted for oestrodiol and oestrone levels there is not an association between free testosterone and endometrial cancer. Transdermal testosterone is associated with endometrial atrophy. [5,14]

Cardiovascular risk - There are conflicting reports for the association of testosterone therapy and cardiovascular risks. There seems to be an optimal range of serum testosterone in postmenopausal women for cardiovascular safety; a study in 639 postmenopausal women measured serum testosterone at baseline and followed cardiovascular events for an average duration of 12.3 years. In age-adjusted analyses, the lowest quintile of serum testosterone was associated with a 1.62-fold increased risk of cardiovascular events (95% CI 1.10 to 2.39)

compared with higher levels. Bioavailable testosterone showed a U-shaped association with events, as the age-adjusted relative risks for the lowest and highest quintiles of bioavailable testosterone were 1.79 (95% CI 1.03 to 3.16) and 1.96 (95% CI 1.13 to 3.41), respectively. The FDA has recently updated its cautions relating to the use of testosterone products for low testosterone due to aging; and requires a labelling change to inform of possible increased risk of heart attack and stroke with use. It needs to be noted that this advice relates to use in men. However, two large studies, the results of which have yet to be fully published, state that the difference in the cardiovascular event rate was not statistically significant between those treated with topical testosterone and those who were not. Again these studies are only in men and are not fully published and have not caused a review of the recent FDA alert.[5,14]

The concerns over liver toxicity seem to only be an issue for the oral administration of testosterone. Transdermal routes of testosterone administration avoid the hepatic first-pass effect and have not been demonstrated to cause hepatotoxic side effects. [5,14]

The effect of exogenous testosterone on lipids in women depends on the dose, route of administration and concomitant oestrogen-progestogen therapy. Current evidence supports the premise that a reduction in HDL cholesterol does not occur with transdermal therapy. The trial assessing the safety of testosterone patches in women did not find any significant difference in serum lipid or lipoprotein profiles. It is still recommended that patients using transdermal testosterone have their lipid profile monitored. [5,14]

Strengths and limitations of the evidence:

Strengths

- Subjects were blinded to treatment.

Limitations

- Evidence in support of gel is limited to one small trial (53 patients completed the study). However, the paper states that the coefficient of correlation between treatments was assumed to be 0.30. Based on this assumption, the minimum number of women needed was 40.
- The results of the trial are based on subjective outcomes.
- The statistical analysis was only carried out on subjects who completed the study, not on the intention to treat population.
- It is unclear whether the increases in frequency of sexual activity, sexual thoughts/fantasies, etc are clinically significant, despite being statistically significant.
- The trial was in patients who had preserved uterus and ovaries, the application requests use in patients who are experiencing HSDD following oophorectomy and therefore does not assess effectiveness in the population that the preparation is proposed to be used in.
- The study is of a very short duration of only 3 months in each arm of testosterone treatment.
- The actual results of the questionnaire are difficult to interpret as the median is reported and is not clear whether this median is for the pooling of the outcomes from both arms.
- It is not clear whether all AEs have been reported or whether only the ones which were

asked specifically about.

- Although the method states that endometrial thickness was measured prior to treatment and at 3 and 6 months, the results of this are not stated in the paper. This is one of concerns of treatment with testosterone.
- The treatment effect for the subgroups were assessed by a post hoc analysis

Summary of evidence on cost effectiveness:

A summary of evidence of cost effectiveness is not available. This product is relatively inexpensive and the issues with its prescribing are related to the efficacy and more importantly the safety.

Prescribing and risk management issues:

There are significant concerns over the dose to be administered. The dose administered can be extremely difficult to measure and could lead to supraphysiologic testosterone levels.

The testosterone levels would need to be monitored closely to avoid the emergence of irreversible AEs – see safety section.

Patients would need to be counselled on the difficulty of measuring an accurate dose, in addition to the safety concerns and the potential for irreversible AEs.

Commissioning considerations:

Comparative unit costs:

The costs of pharmacological therapy for this indication are small. However, the concerns around efficacy and safety are the overriding factor.

Drug	**Example regimen**	**Pack cost**	**Cost per patient per course/ per year (ex VAT)**
Testosterone (Testim®) 1% gel	**Apply 1/10th of 5g tube daily**	**30 x 5g tubes = £32.00**	**£3 per month (£39/year)**
Oestrogen (oral)	1mg to 2 mg daily	84 x 1mg or 2mg = £5.06 – £7.30	From £22 to £32/year
Oestrogen (transdermal)	1 to 2 patches weekly (applied weekly or twice weekly) (various strengths)	8 patches x 25 micrograms/24 hours = £3.42 or 4 patches x 100 micrograms = £7.28	From £45 to £95/year dependent on dose and brand

Tibilone	2.5 mg daily	28 x 2.5 mg =£10.36	£135/year
Costs based on MIMS list prices March 2015.[2] For general comparison only. Inclusion does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

Regular close monitoring of testosterone levels is required.

Productivity, service delivery, implementation:

It is proposed that preparation would be continued in primary care once initiated by specialists. Therefore there would be a decreased impact on secondary care services compared to the testosterone implant which requires administration time by nurses.

Anticipated patient numbers and net budget impact:

The requesting clinician has anticipated a population of 150 for their locality. The clinician has proposed that the use of testosterone gel would be a cost saving due to this being a switch from testosterone implant (which the clinician has estimated costs £166/annum). However, the implants are £9.99 which are administered every 180 days, with an unknown cost of administration).

Innovation, need, equity:

There is a need for psychosocial and pharmacological therapies for patients suffering from HSDD. There are on-going trials assessing the effectiveness and importantly the safety of topical testosterone in patient with HSDD. Whilst awaiting the publication of these trials and the licensing of suitable preparations patients can be managed with other proven safer options.

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Table: Summary of key testosterone RCTs relevant to use in postmenopausal hypoactive sexual desire disorder

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
	Double blind Randomised Crossover design n=60, however only 53 were included in the statistical analysis. (4 excluded due to lack of compliance, 1 due to fracture and 1 due to carcinoma of the uterus and were excluded from further analysis)	**Inclusion criteria:** Post-menopausal women Age 50-65 years (mean 55.4 years) Total loss or significant decrease of libido during the post-menopausal period Preserved uterus and ovaries > 2 months of oestrogen/progestogen hormone therapy Partner Serum testosterone level <2.0 mmol/L No previous andgrogen therapy **Exclusion criteria:** Experienced libido problems prior to menopause Heart disease HTN Malignant disease	**Intervention:** 10 mg testosterone-gel (1% testosterone hydroalcoholic gel testogel) **Comparator:** placebo (equal volume placebo gel) Administered every morning to the outside of the thigh in a thin layer covering approx. 15cm^2 **Duration:** 3 months plus 3 months crossover	No primary outcomes stated.	Sexual life assessed using McCoy questionnaire: Median values for individual items for McCoy questionnaire (range 1 to 7): Frequency of sexual activity baseline = 2 Placebo = 3 Testosterone = 4 (stated p<0.001 for all patients in both arms) Sexual thoughts/fantasies Baseline = 2 Placebo = 2 Testosterone = 3 (stated p<0.001 for all patients in both arms) Sexual enjoyment Baseline = 4 Placebo = 4 Testosterone = 6 (stated p<0.001 for all patients in both arms) Satisfaction with orgasms Baseline = 5 Placebo = 5 Testosterone = 5 p=0.012 for all patients in both arms) QOL assessed using "Psychological general well-being	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes Blinded if possible?: Yes Intention to treat analysis?: No Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 2 evidence based on measurement of patient orientated outcomes Risk of bias: unclear based on outcome measure qualitative rather than quantitative

					questionnaire": Anxiety (5-30) Baseline = 23 Placebo = 24 Testosterone = 27 (p<0.001) Depressed mood (3-18) Baseline = 16 Placebo = 15 Testosterone = 16 (p = 0.382) Positive wellbeing (4-24) Baseline = 15 Placebo = 16 Testosterone = 17 (p=0.01) **Reported adverse events:** Influence on mood, headache, weight, appetite, etc Placebo = 7 patients Testosterone = 6 patients Skin related (acne, facial hair, hair on legs) Placebo = 9 patients Testosterone = 11 patients Vaginal ultrasound for endometrial thickness measured at baseline, 3 months, 6 months. Results were not reported – paper summarises there were no increases in endometrial thickness Total testosterone (nmol/L) Baseline = 0.74 +/- 0.37 Placebo = 0.95 +/- 1.00 Testosterone = 7.8 +/- 5.2 DHT (pmol/L) Baseline = 407 +/- 252	

					Placebo = 302 +/- 272 Testosterone = 993 +/- 1034 Liver enzymes Haemoglobin – not reported Erythropoietin – not reported but paper states levels remain unchanged	

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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