**National Essential Medicine List**
**Tertiary Medication Review Process**
**Component: Dermatology - Isotretinoin**

## MEDICINE MOTIVATION:

### Executive Summary

**Date:** June 2021 (initial review 2011)
**Medicine (INN):** Isotretinoin
**Medicine (ATC):** D10BA01
**Indication (ICD10 code):** Moderate to severe acne (L70)
**Patient population:** Patients with moderate to severe recalcitrant nodular acne.
**Prevalence of condition:** Affects 80-85% of the adolescent population, with 10-20% having moderate to severe acne. Approximately 150 patients per tertiary hospital (~4 050 patients in total) are expected to qualify for this therapy annually.
**Level of Care:** Tertiary
**Prescriber Level:** Specialist - Dermatologist only
**Current standard of Care:** Topical therapy plus doxycycline plus topical therapy (all) or oral contraceptive (females)
**Efficacy estimates:**
There was a modest but not statistically significant reduction in lesion count: ARR = 2.0% (95% CI -4.46% to 8.47%)
Physician's global evaluation: ARR = 13.5% (95% CI 6.22% to 20.83%), NNT = 8 (95% CI 5 - 16)
**Motivator/reviewer name(s): Prof N. Schellack, Mr R. Wiseman**

### Name of author(s)/motivator(s)

Review Update: Prof Natalie Schellack; Mr Roger Wiseman

**Author affiliation and conflict of interest details**

NS – University of Pretoria. No interests to declare.
RW - Liberty Health (Pty) Ltd. No interests to declare.

### Introduction/ Background

Acne is a chronic inflammatory disease of pilosebaceous units resulting from androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization by *Cutibacterium acnes* of hair follicles on the face, neck, chest, and back.[1] There is a paucity of data pertaining to the prevalence of acne in South Africa, however a study conducted in 2014 reported that, out of 6 664 patients, 44.3% had acne.[2]

Acne has a significant effect on the quality of life of those affected, causing decreased self-esteem, severe anxiety and depression. It is frequently found in late adolescence and is associated with significant social and psychological problems. In a large population-based study of 4 744 adolescents, in patients with severe acne, suicidal ideation was twice as frequently reported among girls, and three times more frequently among boys compared to those without acne. In multivariate analysis, suicidal ideation was significantly associated with severe acne (OR 1.80; 95% CI 1.30-2.50). Mental health problems were all found to have significant association with acne.[3]

The current standard of care includes doxycycline, topical tretinoin and oral contraceptives (in females); or combinations of these. It is recognised that these agents are not true comparators to isotretinoin as isotretinoin would only be considered in patients refractory to standard therapy. However, this review seeks to assess the published peer-reviewed data associated with isotretinoin in the management of moderate to severe nodulocystic acne as it is the only agent that targets all pathophysiological causes of acne[4].

## Eligibility criteria for review

**Safety and Efficacy**

- **P** *(patient/population):* patients with moderate to severe acne
- **I** *(intervention):* isotretinoin
- **C** *(comparator):* antibiotics with or without topical agents; oral contraceptives (in females)
- **O** *(outcome):* total lesion count, physician's global assessment, acne grade, depression scores

**Quality of Life**

- **P** *(patient/population):* patients with acne vulgaris
- **I** *(intervention):* isotretinoin
- **C** *(comparator):* topical agents or placebo; oral contraceptives (in females)
- **O** *(outcome):* Quality of life measures

## Methods

**Data sources**

Pubmed, Cochrane database of systematic reviews.

**Search strategy**

Pubmed: ("Acne Vulgaris"[Mesh]) AND "Isotretinoin"[Mesh] Filters: Clinical Trial; Humans)

**Excluded studies**

Excluded after screening title and abstract (n=394)

- Did not address question
- Case reports
- Review
- Not randomised controlled trials

Studies included: n=32

Of the 32 studies:

Excluded:

14: Isotretinoin vs isotretinoin, different dose regimes, formulations
4: Placebo controlled
1: Isotretinoin vs acupuncture
1: Antihistamine as adjuvant
1: Isotretinoin vs isotretinoin plus topical
2: Isotretinoin vs etretinate

1: Isotretinoin on sebum control

Included: Randomised Controlled Trials (RCT) of isotretinoin compared to antibiotic

6: RCT of isotretinoin vs antibiotic

1: Systematic review of isotretinoin vs control

1: Systematic review of isotretinoin treatment for acne and risk of depression

**Quality of life assessment**

**Search strategy**

Pubmed: ("Acne Vulgaris"[Mesh]) AND "Isotretinoin"[Mesh] AND "Quality of Life") - 69 publications

Records retrieved = 69

Of the 69 studies, 8 observational studies were considered for further review[5, 6, 16-21]. Of these, 5 are summarized in Table 1 below

## Results

### 1. Safety and efficacy

The literature review highlighted 6 RCTs, 1 Cochrane Review involving ISO versus antibiotic therapy[7] and one systematic review of ISO treatment for acne and risk of depression[8]. All 6 RCTs were included the Cochrane Review[7], thus the findings of this review are based on the results of the Cochrane Review. Relevant trials, including the papers reflecting the quality of life data, are summarized in Table 1 below.

**Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks.**

The Cochrane Review showed that oral ISO did not reduce the severity of acne as assessed by decrease in total lesion count when compared with oral antibiotics plus any topical agent in patients with moderate to severe acne (3 RCTs, 400 participants): RR 1.01 (95% CI 0.96 to 1.06; $I^2$ = 45.8%). [see Figure 1 for forest plot]

**Improvement in acne severity assessed by physician's global evaluation.**

The Cochrane Review showed that oral ISO improved acne severity when assessed by physician's global evaluation when compared with oral antibiotics plus any topical agent in patients with moderate to severe acne (2 RCTs, 351 participants): RR 1.55 (95% CI 1.00 to 1.32; $I^2$ = 58.76%). [see Figure 2 for forest plot]. In a critique of acne severity assessment tools[22], these particular instruments scored poorly, and hence the clinical relevance of this finding is unclear, and although the pooled measure reached statistical significance the high heterogeneity is concerning.

**Frequency of adverse events**

Only one RCT contributed to the Cochrane Review of the frequency of adverse effects. One serious adverse effect (Stevens-Johnson syndrome) occurred in 192 patients given ISO. [see Figure 3 for forest plot.] The absolute number of events was too low to draw meaningful conclusions from this analysis.

**Frequency of less serious adverse effects**

Oral antibiotics were associated with a lower relative risk of less serious adverse effects, for example dry lips/skin, cheilitis, vomiting, nausea (3 studies, 351 participants): RR = 1.67 (95% CI 1.42 - 1.98; $I^2$ = 0%).

**Isotretinoin and depression**

A meta-analysis by Huang et al[8] reported no association between isotretinoin and depression. The study included 31 controlled or prospectively controlled trials. In six controlled studies, the change in depression scores from baseline was not significantly different between patients receiving isotretinoin treatment and those receiving an alternative treatment (standardized mean difference [SMD] -0.334, 95% CI -0.680 to 0.011). The prevalence of depression after isotretinoin treatment significantly declined (RR 0.588, 95% CI 0.382-0.904). The mean depression scores significantly decreased from baseline (SMD -0.335, 95% CI -0.498 to -0.172).

**2. Quality of Life**

Several small, low quality trials demonstrated changes in various parameters measuring quality of life. Because acne severity follows a variable course and there are no controls, the findings from these studies are difficult to interpret and provide very low quality evidence. The papers are summarized in Table 1 below.

In a case series of patients on ISO reported by Secrest et. al.[6], Skindex-16 scores[23] showed a 4.4-fold improvement (from 39.4 at baseline to 8.9; $P < 0.001$) with the emotional domain score improving 4.8-fold (from 57.7 at baseline to 11.9; $P < 0.001$).

Marron et. al.[16] sought to determine whether isotretinoin in patients with moderate acne was useful in controlling symptoms of anxiety and/or depression and improving quality of life. The mean ± SD score for Dermatology Life Quality Index (DLQI) changed from a baseline of 13.2 ± 3.7 to 4.2 ±2.4 at the end of the study ($p < 0.001$). For the Hospital Anxiety and Depression Scale (HADS), 90 patients at baseline (26.0%) were classified as clinical cases on the Anxiety subscale and 12 (3.5%) on the Depression subscale. These figures reduced to 12 (3.5%) and 6 (1.7%) for Anxiety and Depression, respectively. For SF-36, there was a significant improvement ($p < 0.001$) in the following dimensions: Physical Function, Role Physical, Vitality, Social Function, and Mental Health. There was also a significant improvement ($p < 0.005$) in General Health and Emotional Role Function.[16]

Kaymek et. al.[17] also demonstrated that isotretinoin was associated with an improvement in mean Dermatology Life Quality Index when compared with topical therapy in patients with mild to severe acne (DLQI at 4 months was 3.25 ± 3.48 for ISO vs 7.17 ± 2.59 for control; $p = 0.001$).

## Adverse effects

Adverse effects are predominantly related to dryness[7]. Current evidence suggests that isotretinoin use is not associated with depression[8]. The opposite, in fact, seems to hold true currently. The prevalence of depression significantly declined after isotretinoin treatment (RR 0.588, 95% CI 0.382-0.904)[8].

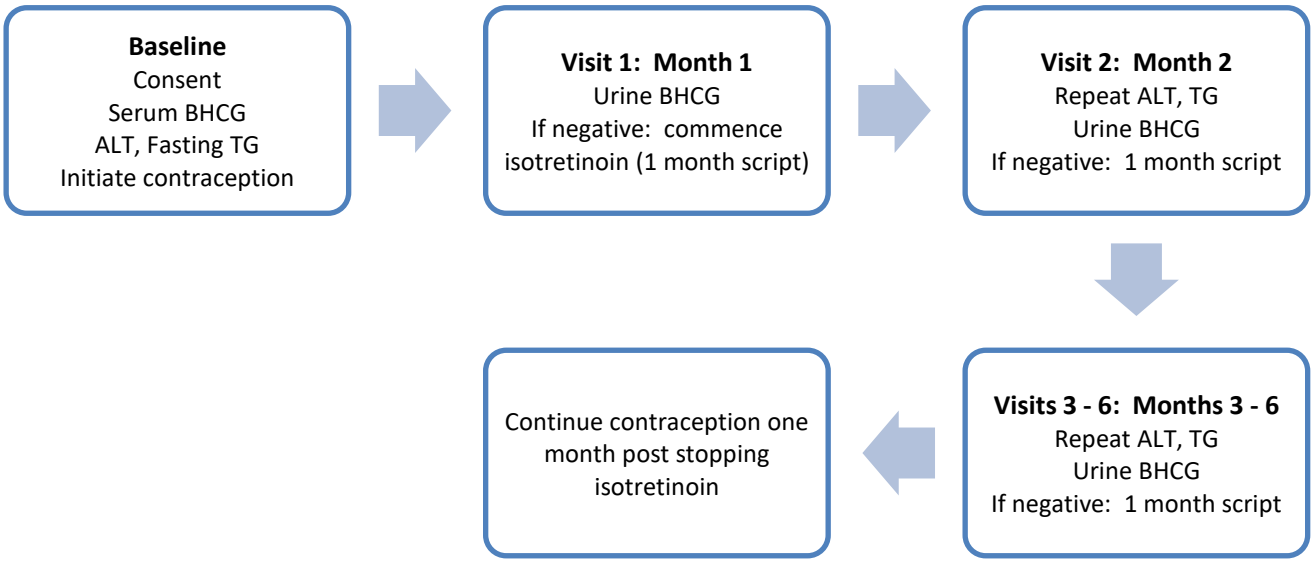
However, some patients with acne may be susceptible to depression, and close monitoring for development of depression of these patients is indicated.

Mild elevation of liver enzymes and fasting plasma lipids are seen in almost all those treated with isotretinoin but uncommonly reach levels above the normal range. The discontinuation of the drug promotes a rapid return to pre-treatment levels[7]. Monitoring of ALT levels and triglycerides is recommended.

Isotretinoin is a potent human teratogen. There is an estimated 20%–35% risk for congenital defects in infants exposed to the drug in utero, including craniofacial, cardiovascular, neurological, and thymic

malformations. About 30%–60% of children exposed to isotretinoin prenatally have been reported to show neurocognitive impairment, even in the absence of physical defects.[9] Mandatory oral contraception in females of childbearing age is indicated.

## Monitoring




## Costs

Both low dose and high dose isotretinoin dosing regimens were costed based on a dose recommended for a 60kg patient. See cost of 4 - 6-month course for both regimens:

Table 1: Cost estimates for different isotretinoin regimens per person

| Agent | Regimen | Dose | Price | | Source* | Cost per day | Cost per month | Cost per 4 months | Cost per 6 months |
|---|---|---|---|---|---|---|---|---|---|
| Isotretinoin (low dose) | 0.5 mg/kg/day for 6 months | 30 mg daily | R8,23 | 20 mg capsule | SEP (Cipla) | R12,42 | R372,72 | R1 490,86 | R2 236,29 |
| | | | R4,20 | 10 mg capsule | SEP (Cipla) | | | | |
| Isotretinoin (low dose) | 0.5 mg/kg/day for 6 months | 30 mg daily | R3,67 | 20 mg capsule | Buy-out WC | R6,07 | R182,00 | R728,00 | R1 092,00 |
| | | | R2,40 | 10 mg capsule | Buy-out WC | | | | |
| Isotretinoin (high dose) | 1 mg/kg/day for 6 months | 60 mg daily | R8,23 | 20 mg capsule | SEP (Cipla) | R24,68 | R740,33 | R2 961,30 | R4 441,95 |
| Isotretinoin (high dose) | 1 mg/kg/day for 6 months | 60 mg daily | R3,67 | 20 mg capsule | Buy-out WC | R11,00 | R330,00 | R1 320,00 | R1 980,00 |

**June 2021*

Since the previous review in 2011, the cost of isotretinoin has decreased in real terms. See table below.

Table 2: Change in price of isotretinoin between 2011 and 2021

| Agent | Strength | Pack Size | SEP in 2011 | Cost /unit | Projected price 2021 adjusted for inflation** | Cost/ unit | % change increase | SEP in 2021 | Cost /unit | % change increase |
|---|---|---|---|---|---|---|---|---|---|---|
| Isotretinoin* | 10mg | 60 | R196, 13 | R3,27 | R316,26 | R4,20 | 61.25% | R251,88 | R4,20 | 28.43% |
| Isotretinoin* | 20mg | 60 | R385,66 | R6,43 | R621,88 | R8,23 | | R493,55 | R8,23 | 27.98% |

*SEP Cipla – Acnetret
**https://inflationcalc.co.za/

Although the price of isotretinoin has increased in nominal terms by approximately 28%, this is much less than would have been expected in real terms (increase of 61.25%) when accounting for inflation. That is, based on the SEP of isotretinoin 10mg (60 pack) of R196.13 in 2011, the projected 2021 price accounting for inflation was estimated to be R316.26 but in, nominal terms, is currently priced at R251.88.

**Sensitivity analysis**

A sensitivity analysis around price was evaluated. Three propose contract price estimates were evaluated (60%, and 40% of Single Exit Price as well as the current buy-out price from the Western Cape).

Table 3: Sensitivity analysis – cost per patient for isotretinoin regimens

| Summary of costs per patient | SEP (Jun 2021) | 60% SEP | Buy-out price WC | 40% SEP |
|---|---|---|---|---|
| Low dose isotretinoin - 4 months | R1 491 | R895 | R728 | R597 |
| Low dose isotretinoin - 6 months | R2 236 | R1 342 | R1 092 | R895 |
| High dose isotretinoin - 4 months | R2 961 | R1 777 | R 1 320 | R1 185 |
| High dose isotretinoin - 6 months | R4 442 | R2 665 | R1 980 | R1 777 |

The Western Cape buy-out price falls between the 60% and 40% of SEP sensitivity analysis results (roughly about 50% of SEP)

**Budget Impact**

Based on data from Groote Schuur Dermatology clinic, and advice from specialists, it is estimated that 150 patients per year would require treatment at Tertiary Hospitals (27 Hospitals), thus, an estimate of 4050 patients was used to calculate budget impact.

Table 4: Budget Impact analysis for isotretinoin regimens for estimated population per annum

| Budget impact of isotretinoin per year | SEP (Jun 2021) | 60% SEP | Buy-out price WC | 40% SEP |
|---|---|---|---|---|
| Low dose isotretinoin - 4 months | R6 038 550 | R3 623 130 | R2 948 400 | R2 415 420 |
| Low dose isotretinoin - 6 months | R9 055 800 | R5 433 480 | R4 422 600 | R3 622 320 |
| High dose isotretinoin - 4 months | R11 992 050 | R7 195 230 | R5 346 000 | R4 796 820 |
| High dose isotretinoin - 6 months | R17 990 100 | R10 794 060 | R8 019 000 | R7 196 040 |

The budget impact range is estimated to be between R2.4 million and R18 million per annum, with the 60% of SEP estimate for all patients using high dose isotretinoin for 6 months calculated to be R10.8

million. At current Western Cape buy-out prices, the national budget impact is estimated to be approximately R8 million per annum. The Western Cape Province further reports that approximately R3 million has been spent on isotretinoin across Groote Schuur, Tygerberg and Red Cross Children's Hospitals over a period of 6.5 years (~R470 000 per year).

**Current standard of care**

The current standard of care includes doxycycline, topical tretinoin and oral contraceptives (in females); or combinations of these. This therapy is used prior to consideration of isotretinoin, and is thus not a true comparator, however it could be expected that these agents may be continued in the absence of a next step in therapy.

Table 5: Costs for current standard of care

| Agent | Regimen | Dose | Price | | Source* | Cost per month | Cost per 4 months | Cost per 6 months |
|---|---|---|---|---|---|---|---|---|
| Doxycycline | 100mg daily | 100 mg daily | R0.29 | 100 mg capsule | Contract | R8.70 | R34.80 | R52.20 |
| Tretinoin | Apply at night | topical | R46.14 | 20g tube | Contract | R92.28 | R369.12 | R553.68 |
| Cyproterone acetate 2mg, ethinyl estrodiol 35mg | 1 tablet daily | 2mg/35mg | R15.18 | 28 tablets | Contract | R16.26 | R65.06 | R97.59 |

**National Contract Price: April 2021*

## Conclusion

The available randomised controlled trials for the use of isotretinoin in the management of moderate to severe acne are old and provide low quality evidence of efficacy but it is unlikely that more robust studies designed to establish the efficacy of isotretinoin will be conducted in future. A Cochrane Review7 of isotretinoin versus oral antibiotics plus topical therapy did not show a reduction in total lesion count (3 RCTs, 400 participants): RR 1.01 (95% CI 0.96 to 1.06; I2 = 45.8%), but did demonstrate an improvement in physician's global assessment [(2 RCTs, 351 participants): RR 1.55 (95% CI 1.00 to 1.32; I2 = 58.76%)]. In addition, a meta-analysis by Huang et al8 did not show an increased risk of depression associated with isotretinoin use. In small observational studies6, 16-19, isotretinoin was associated with improvements in quality of life.

## Recommendation

| Type of recommendation | We recommend against the option and for the alternative | We suggest not to use the option or to use the alternative | We suggest using either the option or the alternative | We suggest using the option | We recommend the option |
|---|---|---|---|---|---|
| | ☐ | ☐ | ☐ | X | |

| | |
|---|---|
| **Recommendation** | It is suggested that isotretinoin be added to the Tertiary/Quaternary Essential Medicine List for dermatologist initiation in patients with moderate to severe acne as a third line treatment option in patients who are refractory to standard of care. |
| **Rationale:** | Notwithstanding the low quality of evidence, there is data to suggest that the use of isotretinoin is not associated with an increased risk of depression, and, in fact may associated with an improvement in QOL. From cost perspective, the direct acquisition cost of isotretinoin has decreased in real terms since the previous review was conducted. Furthermore, isotretinoin has been used in practice for more than 30 years and has become an accepted treatment modality in the management of moderate to severe acne. It is probable that had the Historically Accepted Use medicine template been in existence at the time of the initial review, isotretinoin would have qualified for inclusion on the EML on this basis. |
| **Level of Evidence:** | Level of evidence is low however it does demonstrate that benefits (efficacy and quality of life) outweigh the harm. |
| **Review indicator:** | Low, Level I |

| Evidence of efficacy | Evidence of harm | Price reduction |
|---|---|---|
| X | | |

**VEN status:**

| Vital | Essential | Necessary |
|---|---|---|
| | X | |

| | |
|---|---|
| **Monitoring and evaluation considerations** | The agent should be prescribed and monitored in discussion with a specialist dermatologist (see Isotretinoin Monitoring and Access form) |

*See appendix 2 (Evidence to decision framework)

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**Table 1: Evidence synthesis - summary of relevant clinical trials**

| Citation | Study design | Population (n) | Treatment | Main findings | Comments |
|---|---|---|---|---|---|
| Costa CS, Bagatin E, Martimbianco ALC, et. al. [7]<br><br>Oral isotretinoin for acne.<br><br>Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD009435.<br><br>DOI: 10.1002/14651858.CD009435.pub2 | Systematic review of randomized controlled trials (31 trials included) | Participants: Male and female patients with clinically diagnosed mild to severe acne<br><br>Population: n = 3836 patients (12 to 55 years) | ISO was compared with oral antibiotics plus topical agents.<br><br>Variable doses of ISO were used. | **ISO vs. antibiotics:**<br>(3 trials, n = 400) In patients with moderate or severe acne and assessed outcomes at 20 to 24 weeks of treatment ISO did not show reduction in trial investigator-assessed inflammatory lesion count when compared with antibiotics (RR 1.01 95% CI 0.96 to 1.06). One serious adverse effect of Stevens-Johnson syndrome associated with ISO was noted (RR 3.00, 95% CI 0.12 to 72.98). There is a high degree of uncertainty about these results as they were based on very low-quality evidence.<br><br>Isotretinoin may slightly improve acne severity, assessed by physician's global evaluation (RR 1.15, 95% CI 1.00 to 1.32; 351 participants; 2 studies), but resulted in more less serious adverse effects (RR 1.67, 95% CI 1.42 to 1.98; 351 participants; 2 studies), such as dry lips/skin, cheilitis, vomiting, nausea (both outcomes, low-quality evidence).<br><br>**Dosing** | Evidence was of low to very low quality for most assessed outcomes. |

| Citation | Study design | Population (n) | Treatment | Main findings | Comments |
|---|---|---|---|---|---|
| | | | | Due to heterogeneity, a meta-analysis was not performed. One study (154 participants) reported 79%, 80% and 84% decrease in total inflammatory lesion count 20 weeks of 0.05, 0.1, or 0.2 mg/kg/d of oral isotretinoin for severe acne (low-quality evidence).<br><br>Another trial (150 participants, severe acne) compared 0.1, 0.5, and 1 mg/kg/d oral isotretinoin for 20 weeks and, respectively, 58%, 80% and 90% of participants achieved 95% decrease in total inflammatory lesion count.<br><br>None of the studies reported birth defects. | |
| Tan et. al.[10]<br><br>British Journal of Dermatology; 2014<br><br>A treatment of severe nodular acne: a randomised investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs oral isotretinoin | Phase 3b, Multicentre, randomized, controlled, non-inferiority, investigator blinded study. | Participants: male and female patients with severe nodular acne<br><br>Population: 266 patients.<br>Male = 227<br>Female = 39<br><br>Average age: 19.4 years ± 4.8 years (range 12.0 to 41.0 years) | Oral ISO (0.5mg/kg for 4 weeks with a dose escalation to 1mg/kg daily for the following 16 weeks) vs doxycycline 200mg plus adapalene 0.1%/ benzoyl peroxide 2.5% (A/BPO) gel in severe nodular acne over 20 weeks | Percentage change from baseline in facial nodules, papules/pustules and total lesion counts.<br><br>At week 20, ISO was superior to Doxy in the reduction of nodules (95.6% vs 88.7%), papules/pustules (95.2% vs 79.6%) comedones (92.3% vs 75.9%) and total lesions (92.9% vs 78.2%) (all $p < 0.01$). | |

| Citation | Study design | Population (n) | Treatment | Main findings | Comments |
|---|---|---|---|---|---|
| Huang Y-C & Cheng Y-C[8]<br><br>Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis<br><br>J Am Acad Dermatol 2017<br><br>http://dx.doi.org/10.1016/j.jaad.2016.12.028. | Systematic Review and meta-analysis | Population: 2932 acne patients treated with isotretinoin.<br><br>Patients demographics contained in a supplemental table, but not available as behind a paywall. | ISO was administered at a dose of 0.5-1 mg/kg/day in all studies except for 2 where the doses were 0.1-0.22 mg/kg/day and 2 mg/kg/day. The cumulative isotretinoin dose ranged from 15-150 mg/kg. | Primary outcomes: Prevalence of depression and change in the depression score following isotretinoin therapy.<br><br>Depression score changes from baseline were not significantly different among patients treated with ISO or an alternative therapy (Standard Mean Difference [SMD] -0.334, 95% CI -0.680 to 0.011).<br><br>Depression prevalence following ISO treatment significantly declined (RR 0.588, 95% CI 0.382-0.904).<br><br>For the pre- and post-test scores for ISO treatment, mean depression scores significantly decreased from baseline regardless of the correlation value (SMD -0.335, 95% CI -0.498 to -0.172).<br><br>The funnel plot for change in depression scores in 19 studies showed no publication bias (Egger test, P = .5158) | No RCTs were identified |
| Secrest AM, Hopkins ZH, Frost ZE, et. al.[6]<br><br>JAMA Dermatology 2020 | Longitudinal, retrospective case series study.<br><br>23 November 2016 to 22 January 2019. | Participants: Patients with moderate to severe acne receiving isotretinoin therapy<br><br>Population: 57 consecutive patients. | Patients initially received isotretinoin at a median dose of 0.71mg/kg (females) and 0.55mg/kg (males). Median final dose was 1.05mg/kg (females) and 0.93mg/kg (males) | Primary outcome: Change in mean Skindex-16 score over time.<br><br>Skindex-16 consists of domain scores that assess how symptoms, emotions, | |

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|---|---|---|---|---|---|
| Quality of Life Assessed Using Skindex-16 Scores Among Patients with Acne Receiving Isotretinoin Treatment<br><br>DOI: 10.1001/jamadermatol.2020.2330 | | Male = 31 (54.4%)<br>Female = 26 (46.6%)<br><br>Median age: 17.2 years [IQR 15.8-20.2 years] | Mean cumulative dose was 94.94mg/kg (range 36 - 180mg/kg) in the overall population. | and functioning from the skin issue affect QOL in patients with acne. The overall score averages the 3 domain scores, all of which are normalized to a 0 to 100 scale, where 0 indicates that their skin condition has no impact on QOL and 100 represents maximal impact on QOL for the worse.<br><br>Overall scores decreased from 39.4 at baseline to 17.5 by month 2; a decrease of 22.0 points; P < 0.001). Overall Skindex-16 scores showed a 4.4-fold improvement (from 39.4 at baseline to 8.9; P < 0.001) and Emotional domain scores showed a 4.8-fold improvement (from 57.7 at baseline to 11.9; P <0.001). | |
| Marron SE, Tomas-Aragones L, Boira S.[16]<br><br>Acta Derm Venereol 2013<br><br>Anxiety, Depression, Quality of Life and Patient Satisfaction in Acne Patients Treated with Oral Isotretinoin.<br><br>DOI: 10.2340/00015555-1638 | Prospective, observational, longitudinal study<br><br>June 2005 to September 2011. | Participants: Patients, 16 years and older with moderate acne receiving isotretinoin therapy and who were unresponsive to other combination therapies, including antibiotics.<br><br>Population: 346 patients.<br>Male = 143 (41.4%)<br>Female = 203 (58.6%)<br><br>Mean age ± standard deviation (SD) age was | Oral isotretinoin was administered in weight-dependant doses; a total cumulative dose of 120 mg/kg was given for 30 weeks to patients of both sexes who had moderate acne. Medication was taken twice a day. | Outcomes: Changes from baseline in the Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI) and Health Survey Short-Form–36 (SF-36)<br><br>Mean ± SD score for Dermatology Life Quality Index (DLQI) changed from a baseline of 13.2 ± 3.7 to 4.2 ±2.4 at the end of the study (p < 0.001). For the Hospital Anxiety and Depression Scale (HADS), 90 patients at baseline (26.0%) were | |

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|---|---|---|---|---|---|
| | | 20.7 ± 2.1 years (range 17–33 years). | | classified as clinical cases on the Anxiety subscale and 12 (3.5%) on the Depression subscale. These figures reduced to 12 (3.5%) and 6 (1.7%) for Anxiety and Depression, respectively. For SF-36, there was a significant improvement ($p < 0.001$) in the following dimensions: Physical Function, Role Physical, Vitality, Social Function, and Mental Health. There was also a significant improvement ($p < 0.005$) in General Health and Emotional Role Function. | |
| Kaymak Y, Taner E, Taner Y.[17]<br><br>*Int J Dermatol*. 2009<br><br>Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents<br><br>DOI: 10.1111/j.1365-4632.2009.03806.x | Non-randomised, prospective controlled study.<br><br>September 2006 to May 2007 | Participants: Patients with mild, moderate or severe<br><br>ISO = 37 patients<br>Control 41 patients.<br><br>Mean age<br>ISO = 20.61 ± 1.87 years<br>Control = 20.51 ± 2.01 years | Patients received either isotretinoin at a dose of 0.5–0.8 mg/kg/d for at least 20 weeks, ensuring a cumulative dose of 100 mg/kg, or a topical treatment consisting of either topical antibiotics or topical retinoids. | Change in the following parameters:<br>Disease Severity (DS); Dermatology Life Quality Index (DLQI); Beck Depression Inventory (BDI); Hospital Anxiety and Depression scale–Anxiety (HAD-A,); Hospital Anxiety and Depression scale–Depression (HAD-D); Hospital Anxiety and Depression scale-total (HAD-T).<br><br>Mean DS at 4 months was 0.69 ± 0.62 for ISO vs 1.31 ± 0.66 for control ($p = 0.001$)<br>Mean DLQI at 4 months was 3.25 ± 3.48 for ISO vs 7.17 ± 2.59 for control ($p = 0.001$)<br>Mean BDI at 4 months was 5.86 ± 5.16 for ISO vs 10.6 ± 5.49 for control ($p = 0.01$) | |

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|---|---|---|---|---|---|
| | | | | Mean HAD-A at 4 months was 5.02 ± 3.76 for ISO vs 7.58 ± 3.21 for control (p = 0.002)<br>Mean HAD-D at 4 months was 3.41 ± 3.08 for ISO vs 6.31 ± 3.23 for control (p = 0.001)<br>Mean HAD-T at 4 months was 8.30 ± 6.13 for ISO vs 13.89 ± 5.91 for control (p = 0.001). | |
| Yesilova Y, Bez Y, Ari M, Turan E.[18]<br><br>Acta Dermatovenerol Croat. 2012<br><br>Effects of isotretinoin on social anxiety and quality of life in patients with acne vulgaris: a prospective trial.; 20 (2): 80-3.<br><br>PMID: 22726279 | Single centre, prospective observational study<br><br>January and December 2010 | Participants:<br>Patients with acne vulgaris who were 15 years and older and not taking any medication<br><br>Population:<br>30 patients (19 females and<br>11 males)<br><br>Mean age: 22.6±4.3 (range: 15-<br>31) years.<br><br>Mean duration of acne 69.6±38.3 (range: 12-120)<br>months. | Isotretinoin 0.5-1.0 mg/kg daily for 6 months to reach a cumulative dose of 120 mg/kg. | Change in Liebowitz Social Anxiety Scale (LSAS) and Short Form-36 (SF-36) scores from baseline<br><br>LSAS: The was a statistically significant reduction in 1 of the 6 LSAS domains - Performance avoidance (from 23.2 ± 8.5 to 18.3 ± 7.3 at 65 months, p = 0.01).<br><br>SF-36: The was a statistically significant reduction in 2 of the 8 SF-36 domains:<br>Bodily pain (from 29.0 ± 27.8 to 61.8 ± 28.5 at 6 months, p = 0.001).<br><br>Social functioning (from 58.1 ± 17.6 to 74.5 ± 25.6 p=0.01) | |
| Šimić D, Penavić JZ, Babić D, Gunarić A.[19]<br><br>Psychological Status and Quality of Life in Acne Patients Treated with Oral Isotretinoin. | Single centre, prospective observational study | Participants: Patients with moderate to severe acne<br><br>Population: 127 patients (male =70; female = 57) | All patients received isotretinoin but no dosage information was provided. | Quality of Life as measured by the Dermatology Specific Quality of Life (DSQL).<br><br>Means DSQL score pre- and post-treatment<br>Skin condition 1.38 ± SD 0.83 vs 0.99 ± SD 0.73 (p <0.05) | This paper was published in a supplement. It is unclear whether it was peer-reviewed. |

| Citation | Study design | Population (n) | Treatment | Main findings | Comments |
|---|---|---|---|---|---|
| *Psychiatr Danub*. 2017<br><br>PMID: 28492216 | | Average age = 17.4 years (range 13 to 25 years). | | Personal choices 0.79 ± SD 0.78 vs 0.59 ± SD 0.68 (p <0.05)<br>Behaviour 0.73 ± SD 0.92 vs 0.50 ± SD 0.74 (invalid p-value provided).<br>Relations in the close surroundings 0.41 ± SD 0.68 vs 0.29 ± SD 0.53 (p<0.05)<br>Mental state 1.15 ± SD 1.14 vs 0.81 ± SD 1.03 (p<0.05) | |

**Evidence quality:** The evidence quality is regarded as low to very low for most assessed outcomes.

**Efficacy studies reviewed but not summarized (small patient numbers and all were included in the Cochrane Review):**

1. Oprica C, Emtestam L Hagströmer L, Nord CE. Clinical and Microbiological Comparisons of Isotretinoin vs. Tetracycline in Acne Vulgaris. *Acta Derm Venereol*. 2007; 87: 246-254.[11]
2. Pigatto PD, Finzi AF, Altomare GF, Polenghi MM, Vergani C, Vigotti. Isotretinoin verus minocycline in cystic acne: a study of lipid metabolism. *Dermatologica*. 1986, 172(3): 154-159.[12]
3. Lester RS, Schachter GS, Light MJ. Isotretinoin and tetracycline in the management of severe nodulocystic acne. *Int J Dermatol*. 1985, 24(4): 252-257.[13]
4. Jones DH, Cunliffe WJ, Löffler A. A Comparative Study of 13-cis-retinoic acid and erythromycin therapy in severe acne. *Retinoid Therapy*. 1984.[14]
5. Gollnick HP, Graupe K, Zaumseil RP. Comparison of combined azelaic acid cream plus oral minocycline with oral isotretinoin in severe acne. *Eur J Dermatol*. 2001, 11(6): 538-544.[15]

**Quality of Life Studies not summarized**

1. Tolino E, Skroza N, Proietti I, et al. Efficacy and safety of systemic isotretinoin treatment for moderate to severe acne (insights from the real-life clinical setting) [published online October 9, 2020]. *Dermatol Ther*. doi: 10.1111/dth.14392 (no statistical analysis was provided for the outcomes)[5]
2. Erdoğan Y, Erturan I, Aktepe E, Akyıldız A. Comparison of Quality of Life, Depression, Anxiety, Suicide, Social Anxiety and Obsessive–Compulsive Symptoms Between Adolescents with Acne Receiving Isotretinoin and Antibiotics: A Prospective, Non-randomised, Open-Label Study. 2019. *Pediatric Drugs*. Vol 21: 195 - 202. https://doi.org/10.1007/s40272-019-00340-y (Antibiotic controlled)[20]
3. McGrath EJ, Lovell CR, Gillison F et. al. A prospective trial of the effects of isotretinoin on quality of life and depressive symptoms. *British Journal of Dermatology*. 2010. vol. 163 (6), 1323–1329. DOI 10.1111/j.1365-2133.2010.10060.x (Antibiotic controlled)[21]

**Appendix 1: Forest plots for Cochrane Review: Oral isotretinoin for acne[7]**

**Figure 1: Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks.**

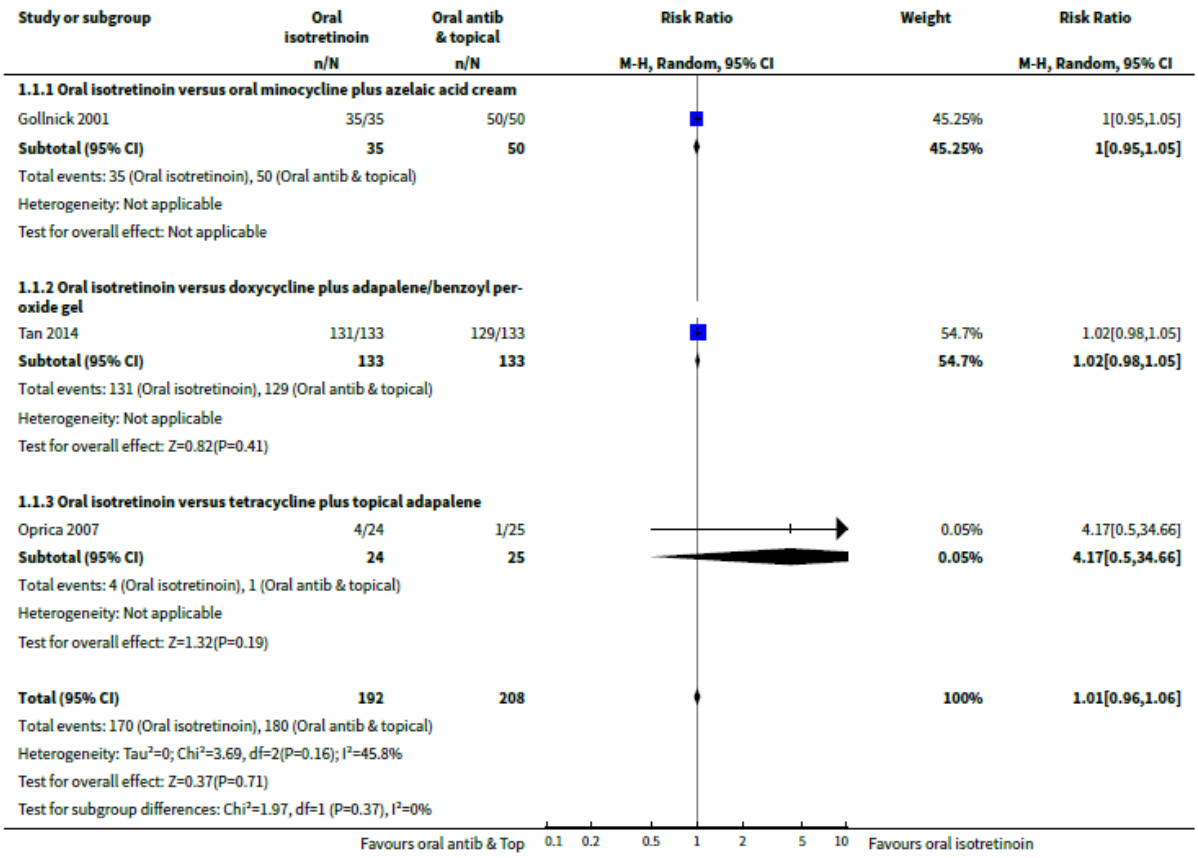
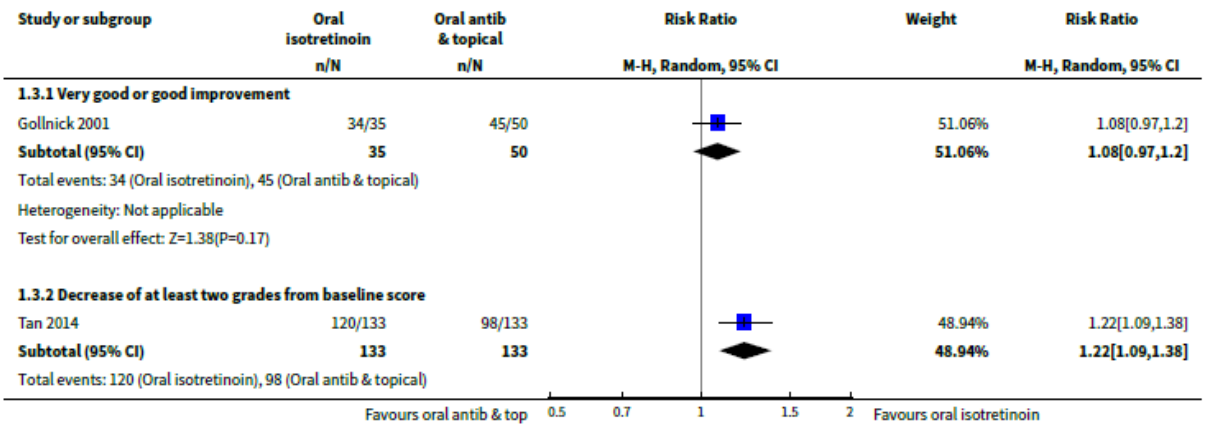



**Figure 2: Improvement in acne severity assessed by physician's global evaluation.**



Cont.

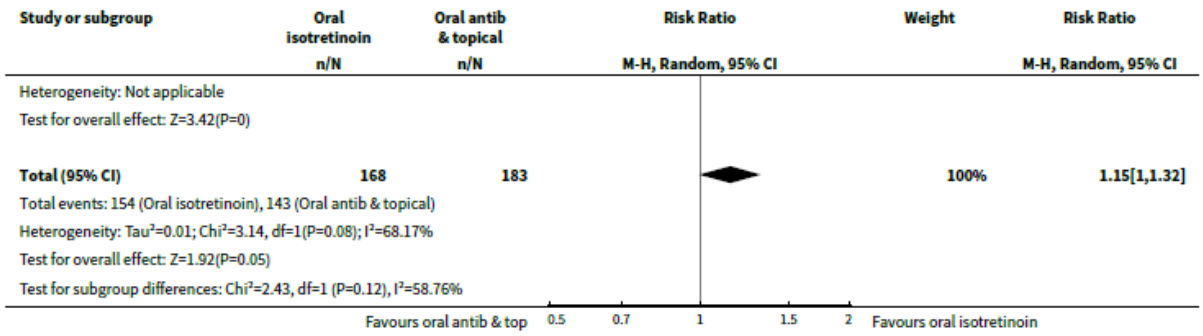



**Figure 3: Frequency of adverse events**

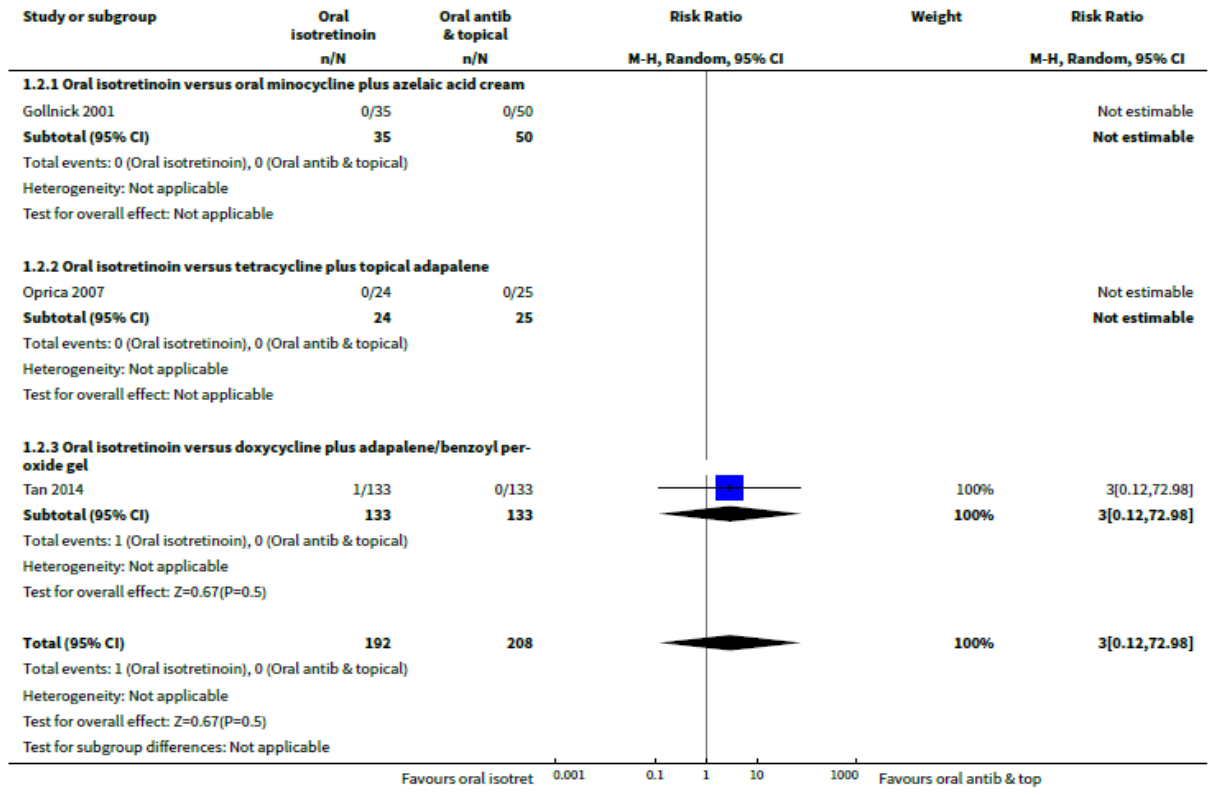
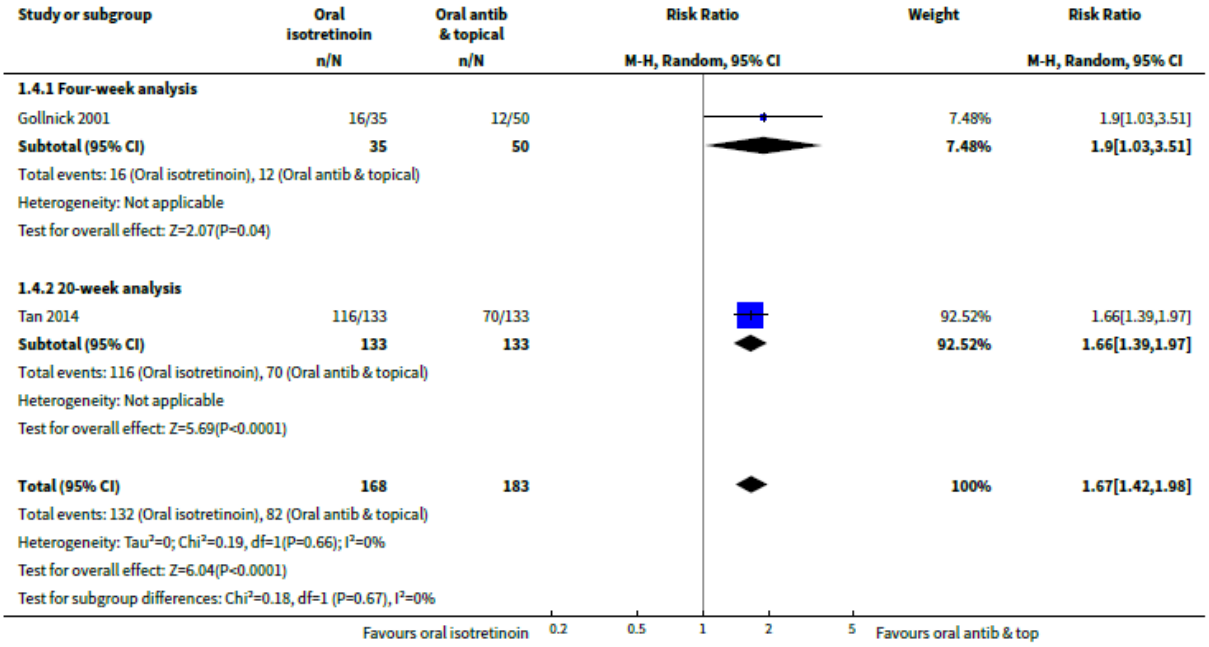


**Figure 4: Frequency of less serious adverse effects**



**Appendix 2: EVIDENCE TO DECISION FRAMEWORK**

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?<br><br><table><tr><td>Confident</td><td>Not confident</td><td>Uncertain</td></tr><tr><td></td><td></td><td>X</td></tr></table></td><td>The data is old and of low quality but it is unlikely that more robust RCTs will be conducted in future. The available evidence found benefit over oral antibiotic therapy when assessed by physician's global evaluation (2 RCTs, 351 participants): RR 1.55 (95% CI 1.00 to 1.32; $I^2$ = 58.76% weak quality of evidence) but found no difference when assessing total lesion count. In uncontrolled observational studies the use of isotretinoin in patients with moderate to severe acne led to improvement QoL scores.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?<br><br><table><tr><td>Benefits out-weigh harms</td><td>Harms out-weigh benefits</td><td>Benefits = harms or Uncertain</td></tr><tr><td></td><td></td><td>X</td></tr></table></td><td>It is uncertain whether benefits outweigh harms. The medication must be used in accordance with the informed consent process, and appropriate monitoring as outlined. Contraceptives should be mandatory for all females of childbearing age.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:<br><br><table><tr><td>Yes</td><td>No</td></tr><tr><td></td><td>X</td></tr></table><br>List the members of the group.<br><br>List specific exclusion from the group:</td><td>No further therapeutic alternative. This is an additional step after failed therapy with topical agents, doxycycline and hormonal contraception (if applicable)</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?<br><br><table><tr><td>Minor</td><td>Major</td><td>Uncertain</td></tr><tr><td></td><td></td><td>X</td></tr></table><br>Is the option acceptable to key stakeholders?<br><br><table><tr><td>Yes</td><td>No</td><td>Uncertain</td></tr><tr><td>X</td><td></td><td></td></tr></table></td><td>Utilised historically in some areas for a number of years, acceptable to dermatologists.</td></tr>
</table>

<table>
<tr>
<td>RESOURCE USE</td>
<td>
How large are the resource requirements?<br><br>
<table>
<tr><th>More intensive</th><th>Less intensive</th><th>Uncertain</th></tr>
<tr><td>X</td><td></td><td></td></tr>
</table>
<br>
No comparative therapy – additional step after topicals, doxycycline, hormonal contraception etc.
</td>
<td>
See costing analysis above.<br><br>
Cost of medicines/ month:
<table>
<tr><th>Medicine</th><th>Cost (SEP)</th><th>Cost (Buy-out)</th></tr>
<tr><td>Isotretinoin low dose (~30mg/day)</td><td>R372,72</td><td>R182,00</td></tr>
<tr><td>Isotretinoin high dose (~60mg/day)</td><td>R740,33</td><td>R330,00</td></tr>
</table>
<br>
Additional costs:
<ul>
<li>Contraceptive cover for duration of treatment. (e.g. oral contraceptive: ~R7/month, or copper IUD ~R160)</li>
<li>Monitoring costs (~R500 for 6 months therapy).</li>
</ul>
</td>
</tr>
<tr>
<td>EQUITY</td>
<td>
Would there be an impact on health inequity?<br><br>
<table>
<tr><th>Yes</th><th>No</th><th>Uncertain</th></tr>
<tr><td></td><td></td><td>X</td></tr>
</table>
</td>
<td>Acknowledge that access to treatment will only be for eligible patients at tertiary level which may potentially impact equity however efforts will be made to strengthen appropriate down referral pathways to try to facilitate access.</td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>
Is the implementation of this recommendation feasible?<br><br>
<table>
<tr><th>Yes</th><th>No</th><th>Uncertain</th></tr>
<tr><td>X</td><td></td><td></td></tr>
</table>
</td>
<td>The intervention is utilised currently in tertiary centres and the incremental cost is lower than when evaluated previously. As it is already in use, the budget impact is likely to be minimal unless approval leads to indication creep.</td>
</tr>
</table>