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**Review Article**

# Expert dialogue on topical minocycline gel in acne vulgaris: minologue India

**Malavika Kohli[1], Prabhakar Sangolli[2], Sanjeev Aurangabadkar[3], Rajetha Damisetty[4,5], D. A. Satish[6], Shrichand G. Parasramani[7,8], Anil Ganjoo[9,10], Deepak Jakhar[11], Anand Nott[12], Miti Gandhi[13]*, Dhiraj Dhoot[13], Kruttika Chitnis[13], Hanmant Barkate[13]**

[1]Department of Dermatology and Aesthetics, Skin Secrets, Mumbai, Maharashtra, India
[2]Department of Dermatology, SSIMS and RC, T-Begur, Bangalore, Karnataka, India
[3]Department of Dermatology, Dr. Aurangabadkar's Skin and Laser Clinics, Hyderabad, Telangana, India
[4]Department of Dermatology and Cosmetology, Hyderabad, Telangana, India
[5]Oliva Chain of Hair and Skin Clinics, Hyderabad, Telangana, India
[6]Department of Dermatology, Skin Cosmetic and ENT Care Center, Bangalore, Karnataka, India
[7]Department of Dermatology, Lilavati Hospital, Mumbai, Maharashtra, India
[8]Department of Dermatology, Hinduja Hospital, Mumbai, Maharashtra, India
[9]Department of Dermatology and Laser Surgery, Skinnovation Clinics, New Delhi, Delhi, India
[10]SAARC Association of Aesthetic Dermatology, Vikas Puri, New Delhi, Delhi, India
[11]Department of Dermatology, North Delhi Municipal Corporation Medical College and Hindu Rao Hospital, New Delhi, Delhi, India
[12]Department of Dermatology, Skin Research Center, Chennai Kauvery Hospital, Chennai, Tamil Nadu, India
[13]Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Miti Gandhi,
E-mail: miti.gandhi@glenmarkpharma.com



## ABSTRACT

Acne vulgaris is a common skin disorder with a global prevalence of about 9.4%. Oral antibacterials are recommended but they are associated with potential systemic side effects. Topical minocycline 4% has been recently approved by the United States Food and Drug Administration (US-FDA) for the management of moderate to severe acne. Although efficacy and safety are established, little is known of its real word usage. To review and appraise existing literature and make recommendations on the real world usage and positioning of topical minocycline 4% in acne management. The minocycline 4% consensus was developed by nine acne experts and was evidence-based on a review of recent topical minocycline 4% literature. A total of 11 questions were discussed regarding different domains like positioning of topical minocycline in acne management as monotherapy and combination therapy, safety and use in special population. Several recommendations were given regarding topical minocycline use like: no monotherapy use; consider use in combination with other anti-acne treatments like isotretinoin, adapalene and benzoyl peroxide; not recommended to be combined with systemic antibiotics; low chances for hyperpigmentation; use of sun protection measures; consider risk benefit ratio in pregnancy; use in lactation not recommended; and can be used only in children >9 years of age. This consensus has discussed and answered many real world usage questions and place in therapy for topical minocycline in acne management and finds it a useful addition to the existing armamentarium.

**Keywords:** Topical, Minocycline, Acne, Recommendations, Consensus

## INTRODUCTION

Acne vulgaris (AV) is one of the most common skin disorder, majorly affecting pre-adolescent and adolescent age group with a global prevalence about 9.4%.[1,2] Though multifactorial, but *Cutibacterium acnes* (formerly called *Propionibacterium acnes*) and inflammatory processes play critical roles in the occurrence of AV and hence antibacterials are routinely prescribed for its treatment.[3,4] Oral antibacterials, targeting both, *C. acnes* and the inflammatory processes are recommended in moderate to severe acne but they have been linked to possible side effects like hypersensitivity reactions, gastrointestinal (GI) upset and others that may appear systemically.[4,5] The use of topical antibacterials like clindamycin and erythromycin that are being commonly prescribed is becoming limited due to an increase in resistance.[6] However, tetracyclines have shown a low resistance to *C. acnes* comparatively and out of them minocycline has been noted to have the lowest; however, potentially serious systemic adverse effects (SAE) associated with its absorption remain a significant concern.[4,6,7]

Recently, topical minocycline 4% was approved by the US Food and Drug Administration in September 2019 and Drug Controller General of India in 2022 for the management of moderate to severe acne.[8,9] Although the efficacy and safety of topical minocycline is extensively documented in landmark clinical trials, very little is known about real-world usage, such as safety and cutaneous tolerability, positioning as monotherapy or combination therapy.

Recommendations given by physicians and experts with experience and arising from consensus survey/meetings, by means of detailed and validated methods are capable of giving guidance on practical aspects and providing useful information.[10] To build up the existing evidence on topical minocycline 4%, a group of experts in dermatology from India, with experience of >10 years in acne management along with ≥6 months in topical minocycline 4%, gathered together to appraise the clinical and real world scenarios and aspects of treatment for which the information in the literature was considered to be lacking.

## METHODS

The minocycline 4% consensus was developed by nine acne experts and was based on a review of recent, international and evidence-based topical minocycline 4% literature. The information from these literature was simplified and harmonized based on consensus and the clinical experience of the authors, and are supported by recently published literature. Complete methodology is depicted in Figure 1.

## DISCUSSION

A total of 11 questions were discussed regarding different domains like positioning of topical minocycline in acne management as monotherapy and combination therapy, safety and use in special population. The experts appraised the literature and gave their recommendations after being asked these questions. Expert recommendations regarding topical minocycline in acne management have been mentioned in Table 1.

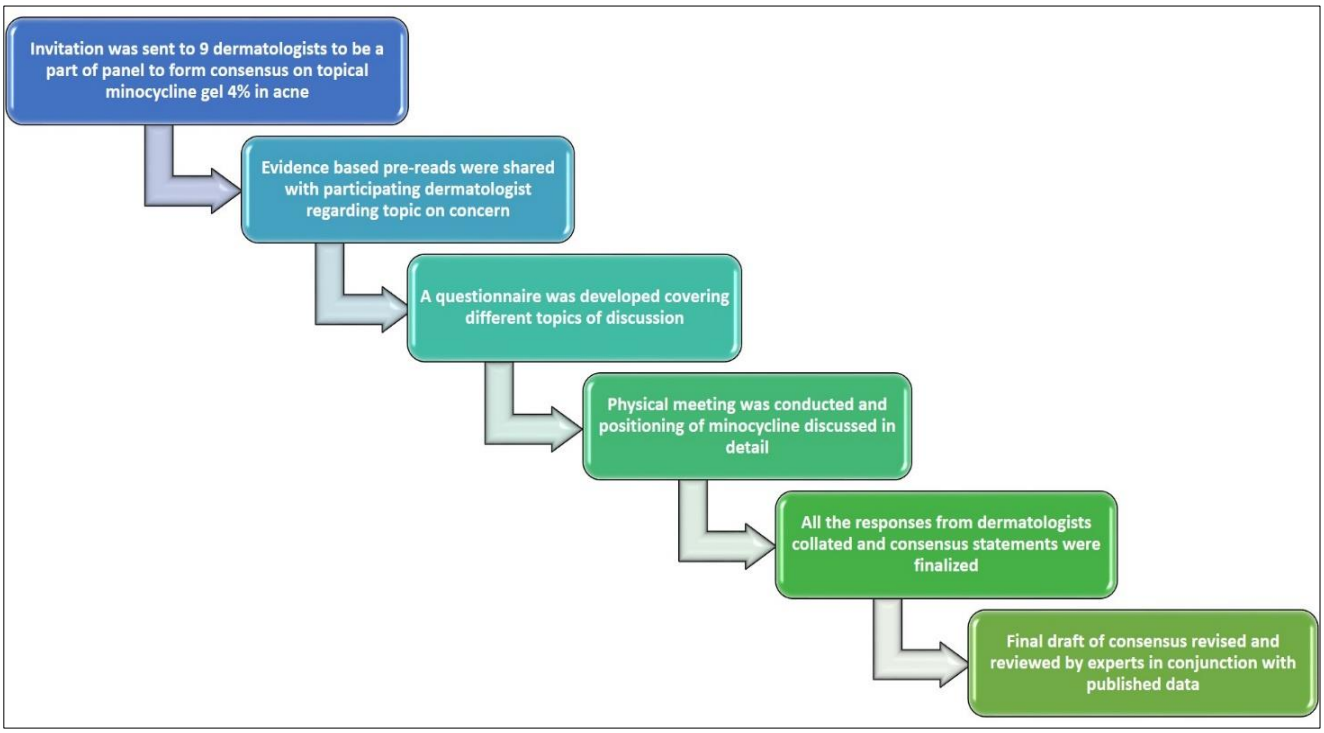


**Figure 1: Methodology.**

**Table 1: Expert recommendations regarding topical minocycline in acne management.**

| S. no. | Position of topical minocycline | Expert recommendation |
|---|---|---|
| **1** | As monotherapy | It is not recommended to prescribe topical minocycline as monotherapy |
| **2** | As combination therapy with isotretinoin | Although combination therapy can be practiced, physician's discretion is warranted |
| **3** | As combination therapy with Adapalene or benzyl peroxide (BPO) | Topical minocycline can be considered in combination therapy with either of the drugs |
| **4** | In combination with systemic antibiotics | It is not recommended to combine with systemic antibiotics |
| **5** | Safety in terms of hyperpigmentation | Experts opine that hyperpigmentation would not be an issue in real world practice with topical minocycline |
| **6** | Safety in terms of phototoxicity | Sun protection measures must be taken and exposure to natural or artificial light (tanning beds or UVA/B treatment) must be minimised or avoided while undergoing treatment with topical minocycline |
| **7** | Use in pregnancy | The risk benefit ratio must be examined before prescribing topical minocycline to pregnant females |
| **8** | Use in lactation | Treatment with topical minocycline during lactation is not recommended |
| **9** | Use in children | Topical minocycline 4% is approved in patients 9 years and above for the management of moderate to severe acne but its safety and efficacy is not established for children <9 years of age |

## POSITIONING OF MINOCYCLINE 4% IN ACNE MANAGEMENT

### *Topical minocycline 4% gel as monotherapy*

Topical minocycline 4% as monotherapy has been studied as part of three randomized controlled phase III trials over 12 weeks. In these trials, it was shown to have an effect on moderate to severe acne with an improvement of inflammatory and non-inflammatory lesions.[11,12] Its efficacy as monotherapy has been established further in long term extension study for 52 weeks of treatment.[13] In all these studies, once-daily topical minocycline 4% was well tolerated with minimal adverse events.[11-13]

Based on the results of the phase 3 studies, monotherapy with topical minocycline seems like a promising prospect. However, because of increased risk of bacterial resistance, monotherapy with topical antibiotics is not recommended by major guidelines.[4,14]

Considering these facts and the scenario of rampant and irrational use of antibiotics in India, experts recommended against the use of monotherapy with topical minocycline in the management of acne.

### *Topical minocycline 4% gel as combination therapy*

*Combination with isotretinoin*

Systemic isotretinoin is considered the drug of choice for the treatment of not only severe nodulocystic acne but also moderate acne that fails to respond to conventional therapy.[15-18] Although, it has been associated with a number of cases of pseudotumor cerebri (PTC), some of which have been reported with concomitant use of tetracyclines.[19,20] Evidence has suggested that minocycline itself has potential to cause PTC and also, some case reports of concomitant use of isotretinoin and tetracycline have shown to develop symptoms of PTC.[20-22] Studies by Moskowitz et al and Tintle et al suggested periodic ophthalmic examination and careful surveillance for PTC in patients receiving vitamin A derivative with oral minocycline.[23,24] As per the National Ambulatory Medical Care Survey (NAMCS) data, co-prescription of isotretinoin and tetracycline was rare and could be observed only in a miniscule fraction of all acne visits.[25] Since systemic use of minocycline and isotretinoin has shown to increase risk of PTC, it is important to keep the risk in mind while combining isotretinoin with topical minocycline.

A pharmacokinetic study had shown that topical minocycline 4% has 730-765 times less systemic exposure than oral minocycline.[26] In the open label extension trial of minocycline foam 4%, headache events (usually a symptom of pseudotumor cerebri) were not considered serious and did not lead to study discontinuation.[27]

Till the time of writing this manuscript, two clinical trials were registered regarding concomitant use of topical minocycline and isotretinoin but no results were posted.[28,29] Hence in view of scarcity of data, experts recommended physician's discretion in case of its use in acne patients.

*Combination with adapalene/BPO*

Topical therapies are backbone of acne management and multiple guidelines recommend the use of topical therapies in combination with other topical or systemic anti-acne therapies in majority patients with acne.[4,14] Multiple

studies have shown advantage of combining topical antibiotics like clindamycin, lymecycline and doxycycline with other anti-acne agents like adapalene and BPO, in the management of acne.[11-13,30-33]

Despite their proven efficacy and safety, widespread use of clindamycin and erythromycin has resulted in the development of drug resistance as well as *C. acnes* strains with cross-resistance to different antibiotics.[6,34,35] Tetracycline class of drugs have low resistance with minocycline having lowest resistance and low risk of cross resistance.[7] MIC values of topical minocycline against various strains of *P. acnes* are lower compared to other antibiotics. When the $MIC_{90}$ values of antibacterials were compared, it was found that topical minocycline 4% is more active by 4-fold; 8-fold; and >32-fold than bacitracin and tetracycline; clindamycin; and neomycin, erythromycin, and fusidic acid respectively.[36] In a study by Mendosa et al, only 1% isolates of *P. acnes* were resistant to minocycline.[34]

Currently, there is only one phase 2 study of combination of 3% minocycline and 0.3% adapalene topical foam formulation (FCD105) for the treatment of moderate-to-severe acne. In that study, authors noted that FCD105 foam showed more absolute change in inflammatory lesion count from baseline and IGA treatment success, which was statistically significant compared to vehicle foam. In terms of absolute change in non-inflammatory lesions at week 12, FCD105 showed a bigger change than vehicle foam. In the same study, FCD105 was seen to be well tolerated and majority (≥93%) of the local signs and symptoms were reported as "none" or "mild" at week 12.[37] There are no clinical studies which have demonstrated the efficacy and safety of combination of topical minocycline with BPO.

Although, the combination of topical antibiotics like clindamycin and erythromycin have exhibited proven benefit in terms of reducing inflammatory and non-inflammatory lesions of acne, the increasing resistance limits their use. Hence, considering increasing bacterial resistance to other antibiotics and the proven efficacy and safety of topical minocycline in patients with moderate to severe acne, it could be considered as agent of choice in combination therapy.

When combining with adapalene, experts opined to apply topical adapalene first in the evening and wash face after an hour, followed by application of topical minocycline after 2-3 hours (1-2 hours before bedtime) since both the drugs are recommended to apply at night. Since no photoxicity has been reported with topical minocycline 4%, experts recommend that topical minocycline can be applied during the day and topical adapalene at night.[38]

*Combination with oral antibiotics*

According to guidelines it is not recommended to combine topical and oral antibiotics for management of acne to limit antibiotic use and decrease chance of development of resistance.[4,14] Hence, it is advisable to prescribe topical minocycline 4% gel first so as to avoid the systemic side effects of oral minocycline and other oral antibiotics.

## SAFETY PROFILE OF TOPICAL MINOCYCLINE 4%

Oral minocycline has been proven beneficial in moderate to severe acne across the available clinical evidence and it can be used as first line.[4,39] Nonetheless, there are still legitimate concerns with systemic adverse events associated oral minocycline which limits its usefulness.[33] Hence topical formulation of minocycline is desirable. In the landmark phase 3 and long term extension trials, topical minocycline 4% was well tolerated with minimal side effects and discontinuation rate.[39,40,27]

While drug interactions with systemic minocycline have been documented, Drugs.com reports six drug interactions with topical minocycline as of now.[41,42] Additionally, topical minocycline has the benefit of a targeted local application, improving skin absorption and effectiveness while preventing side effects associated with oral and IV forms.[39] Moreover, the pharmacokinetic benefits of topical administration were amply demonstrated by studies where various topical minocycline concentrations (1%, 3% and 4%) showed about 730-1500 times lower level in the system than those of extended-release minocycline capsules.[26,43] Adverse events reported so far with topical minocycline have been noted to be mostly mild to moderate and not seen to be as severe as systemic minocycline. Also, the rates of the adverse effects like erythema, dryness, hyperpigmentation, skin peeling, and itching was similar to the vehicle.[38] But still, hyperpigmentation and photo toxicity remained the adverse events of concern owing to class effect.

***Topical minocycline 4%: skin hyperpigmentation***

Skin hyperpigmentation is one of the major concern associated with minocycline use.[44-47] Hyperpigmentation associated with minocycline is dose dependent and is commonly observed in patients receiving a total dose of 100–200 mg/day.[44-47] A cumulative minocycline dosage of at least 70–100 g appears to be important in the development of hyperpigmentation.[45] Incidence of hyperpigmentation associated with minocycline ranges between 3–15%.[44-47] In almost all cases, the pigmentation resolved after the drug is stopped; however, several months may elapse before complete resolution is achieved. There are 4 patterns of minocycline induced hyperpigmentation with type I and II, which is blue black and blue grey discoloration respectively, being most common. The pigmentation appears because of accumulation of minocycline or a minocycline degradation product chelated with haemosiderin, ferritin or iron in dermal macrophages.[45]

From above discussion it is clear that minocycline associated hyperpigmentation is dose dependent in nature,

is harmless and reversible, appears because of accumulation of minocycline or degradation products in dermal macrophages and is seen in ~15% of patients.

In phase 3 studies, there was no difference in incidence of hyperpigmentation between topical minocycline 4% versus vehicle (14.4% versus 17.3%). In most cases, the pigmentation was reported as post-inflammatory hyperpigmentation (PIH), the incidence which is significantly increased in patients with acne. Various studies reported the incidence of PIH in patients with acne in the range of 50–70%.[48,49] Another important consideration with topical minocycline is its dermal absorption. In phase 1 study high concentration of minocycline was seen in epidermis and sebaceous appendage (560 ug/ml) and much lower concentrations were achieved in dermis skin layer (17 ug/ml).[50] In another phase 1 study it was seen that topical minocycline 4% when applied once a day up to a maximum of 4 g once-daily for 21 days compared to a single oral dose of about 1 mg/kg showed ~750 times lower exposure systemically.[26]

Considering all the above facts, experts were of opinion that hyperpigmentation should not be an issue in real world practice with topical minocycline 4% because of lower systemic exposure, less delivery to dermis; the major site of hyperpigmentation and PIH.

***Topical minocycline 4%: photo toxicity***

Tetracycline class of drugs are associated with photo toxicity, however in clinical studies, no photo toxicity has been demonstrated with oral minocycline.[44,51] No evidence of clinically relevant photo toxicity, photo allergy, potential of sensitization and skin irritation was noted with topical minocycline 4% in phase 1 studies.[38,52]

Although topical minocycline 4% did not induce photo toxicity in clinical studies, it is recommended to avoid or keep exposure to natural or artificial light (tanning beds or UVA/B treatment) to a minimum while undergoing applying topical minocycline. Sun protection measures are recommended while going outside during treatment with topical minocycline 4%.

## SPECIAL POPULATION

***Pregnancy***

The clinical evidence for topical minocycline 4% use during pregnancy is insufficient to assess any potential risk of serious birth abnormalities, miscarriage, or other unfavorable mother or fetal outcomes from the medicine. Following once daily topical application for 21 days, systemic absorption of topical minocycline 4% in humans in clinical tests was ~750 times lower than that of oral minocycline at a dose of 1 mg/kg. It is not anticipated that maternal use of topical minocycline 4% will significantly increase fetal exposure to the antibiotic due to limited systemic exposure.[8]

Nonetheless, because of paucity of data specialists indicated that the risk benefit ratio should be examined before giving topical minocycline to pregnant females.

***Lactation***

After oral administration of tetracyclines, which includes minocycline, the drugs have been seen to be present in breast milk. Whether or not minocycline is present in human milk after topical administration is unknown. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, treatment with minocycline 4% during lactation is not recommended.[8]

***Pediatric use***

Topical minocycline 4% is approved in patients 9 years and above for management of moderate to severe acne. In children less than 9 years of age, the safety and efficacy of topical minocycline for acne has not been established. Tetracycline class of drugs have been seen to cause yellow-gray-brown discoloration of teeth permanently and inhibition of bone growth if used in patients below 8 years of age.[8]

## PLACE IN THERAPY

Topical minocycline 4% is approved for the treatment of inflammatory lesions of non-nodular, moderate to severe acne in adults and pediatric patients aged ≥9 years.[8]

Multiple acne guidelines around the world recommends use of combination therapy to target multiple pathogenic factors associated with acne.[4,14] Antibiotics are recommended as first line agent in management of patients with moderate to severe acne in combination with either topical retinoid, BPO or even with isotretinoin.[4,14] Oral antibacterials have been used as one of the main treatments for acne, but due to major concerns like the risk of systemic AEs and increase in bacterial resistance their therapeutic potential is limited. Topical antibiotics like clindamycin or erythromycin are most frequently preferred antibiotics in clinical practice, however increase cases of resistance is being reported to these agents thus limiting their usefulness.

Topical minocycline 4% is the first topical minocycline product which has demonstrated long term efficacy and safety in patients with moderate to severe acne.[37-39] It has also shown lower rates of resistance as well as a potent antibacterial activity *in vitro* in *C. acnes* isolates.[36] The potential of systemic toxicity seen commonly with oral antibacterials would be significantly less with topical formulation due to minimal absorption and accumulation of minocycline systemically.[39,49]

The phase III clinical trials conducted with topical minocycline 4% once a day have shown significant improvement in moderate to severe acne in pediatric and

adult patients. Reductions were seen in both inflammatory and non-inflammatory lesions in both short and long period studies.[36-40] On the subject satisfaction assessment, majority of patients were recorded to be satisfied or highly satisfied with topical minocycline 4%, in terms of its ease of use.

Topical minocycline 4% in the open label study over 52 weeks showed that all the SAEs and most TEAEs were not related and overall was well tolerated. Topical minocycline 4% was not associated with any clinically significant phototoxicity, photoallergy, skin sensitization and skin irritation all of which are potential side effects of oral antibacterials and/or other topical agents.[4,52]

A recent randomized, open-label, double-arm study conducted by Shah et al compared topical minocycline 4% to topical clindamycin 1% in acne. Results of the study showed that after 12 weeks, topical minocycline was superior to topical clindamycin in terms of efficacy and had a favorable safety profile.[53]

Since the cost of therapy is also an important consideration in real world practice, it is imperative to reflect upon the price and cost-effectiveness of a drug. The price of topical clindamycin in Indian market is approximately Rs. 180-200 for 15-20 grams while the price of topical minocycline 4% gel is about Rs. 425 for 15 grams.[54] Even though, topical minocycline is slightly higher in price than clindamycin, the background of rising resistance to topical clindamycin and better efficacy and safety of topical minocycline must be considered.

Hence, looking at the overall efficacy and safety of topical minocycline 4%, itis an attractive option in current scenario for management of patients with acne.

The limitations of this consensus are that the recommendations are the experts' opinion and physicians should use their discretion while prescribing.

## CONCLUSION

In this consensus, many real world usage questions have been addressed and topical minocycline's place in acne therapy has been discussed. Considering the available clinical evidence, experts have given several recommendations for usage of topical minocycline like recommendation against monotherapy use in acne; consideration for use in combination with isotretinoin, adapalene and benzyl peroxide; recommendation for prescription of topical before systemic minocycline; opining regarding low chances of hyperpigmentation in real world; recommendation to use sun protection measures and minimizing/avoiding light exposure while on treatment; recommendation to consider risk versus benefit ratio in pregnancy and not to use in lactation; and recommendation to use only in children 9 years and above as approved. Overall, it was concluded that topical minocycline is a useful addition to armamentarium of anti-acne agents for the management of inflammatory lesions of non-nodular, moderate to severe acne in adult and pediatric patients aged ≥9 years.

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