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ADIS DRUG EVALUATION

Topical Minocycline Foam 4%: A Review in Acne Vulgaris

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Abstract

Topical minocycline foam 4% (Amzeeq™) is approved in the USA for the treatment of inflammatory lesions of non-nodular, moderate to severe acne vulgaris (acne) in patients aged ≥ 9 years. It was developed to minimize systemic minocycline absorption and toxicity, and its high lipid content allows efficient drug movement through sebum and into affected sites. The favorable in vitro resistance profile of oral minocycline seen in *Cutibacterium acnes* (*C. acnes*) isolates was maintained with topical minocycline foam 4%. In 12-week, phase III clinical trials, once-daily topical minocycline foam 4% significantly improved both inflammatory and noninflammatory lesions relative to foam vehicle in patients aged ≥ 9 years with moderate to severe acne and was reported by most patients to be satisfactory or highly satisfactory to use. Extension trial data indicated that topical minocycline foam 4% continued to be effective for up to 52 weeks' therapy. Topical minocycline foam 4% was generally well tolerated in these patients, with most adverse events (AEs) and all serious AEs considered to be unrelated to treatment. Cutaneous AEs were uncommon, and findings from a dermal safety study showed that topical minocycline foam 4% did not have any effects related to phototoxicity, photoallergy, skin sensitization and skin irritation. Topical minocycline foam 4% is thus a useful addition to available treatment options for the management of inflammatory lesions of non-nodular, moderate to severe acne in adult and pediatric patients aged ≥ 9 years.

Topical minocycline foam 4%: clinical considerations in acne vulgaris

First topical minocycline product; favorable in vitro resistance profile of minocycline in *C. acnes* is maintained

Minimal systemic absorption and accumulation

Improves inflammatory and noninflammatory skin lesions

Generally well tolerated

Enhanced material for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.12089649.

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1 Introduction

Acne vulgaris (acne) is an extremely common inflammatory skin condition [1]. Affecting the pilosebaceous unit, acne is characterized by both inflammatory and noninflammatory lesions in addition to some scarring [2]. Affected individuals often have a significant psychological burden, particularly because the face is the most frequently affected area of the body due to it having the highest concentration of pilosebaceous units [3]. In many instances, acne is chronic (as seen by frequent relapses) and requires long-term treatment [4]; while more prevalent among adolescents and young adults, acne may continue through adulthood [1].

The four major factors contributing to acne development are sebum hypersecretion (often alongside qualitative and quantitative alterations in sebum composition [5]), abnormal keratinocyte proliferation and differentiation in hair follicles, overgrowth of skin microflora [*Cutibacterium acnes* (*C. acnes*), formerly known as *Propionibacterium acnes*], and host inflammatory response [4]. These factors are synergistic and their interplay drives acne pathogenesis: *C. acnes* digests sebum triglycerides via lipases into free fatty acids (thereby triggering downstream inflammatory responses) and forms biofilms in sebaceous sites, promoting hyperkeratinization and comedone formation [6]. The

subsequent host inflammatory response leading to follicular wall rupture and tissue destruction underlies the characteristic lesions seen in acne [6].

With bacteria therefore having a significant role in acne pathogenesis, antibacterials are frequently prescribed for acne treatment [1]. Moderate to severe acne is often treated with oral antibacterials, which may target both *C. acnes* and the inflammatory processes contributing to acne [7]. However, oral antibacterials are associated with systemic side effects, including gastrointestinal (GI) disturbances and hypersensitivity reactions [1]. While topical formulations of clindamycin and erythromycin are widely available, their prolonged use has been associated with increasing levels of antibacterial resistance; cross-resistance of *C. acnes* to the two antibacterials is also common [8]. Tetracyclines have lower resistance rates, with minocycline (a second-generation tetracycline) having the lowest [8, 9]; however, oral minocycline has been associated with serious adverse events (SAEs) such as renal or hepatic failure, or drug-induced lupus [1]. There is therefore a need for an antibacterial treatment that is both effective and safe over long periods in both adults and pediatric patients.

Developed to minimize systemic toxicity, topical minocycline foam 4% (Amzeeq™) is the first topical minocycline product available, and is approved in the USA for the treatment of inflammatory lesions of non-nodular, moderate to severe acne in patients aged ≥ 9 years [10]. This article reviews pharmacological, clinical efficacy and tolerability data relevant to the use of topical minocycline foam 4% in this setting.

2 Pharmacological Properties of Topical Minocycline Foam 4%

2.1 Composition

Topical minocycline foam 4% is an oil-based suspension dispensed as foam from a pressurized can [10, 11]. One gram of product contains micronized minocycline 40 mg (equivalent to minocycline hydrochloride 43 mg). The foam vehicle is composed of natural oils [10] that stabilize and protect minocycline from degradation while providing an occlusive effect to help retain skin moisture [11]. The hydrophobic nature of the foam vehicle effectively decreases the viscosity of sebum at skin temperature, (as observed in vitro through rheometry) and enables efficient drug movement through sebum-filled hair follicles to the pilosebaceous units [11]. Topical minocycline foam 4% showed high miscibility in vitro with artificial human sebum at 35 °C (95°F) when seen under polarized light microscope; the juxtaposed samples of topical minocycline foam 4% and sebum appeared to merge, with minocycline microcrystals migrating into the sebum. By contrast, the borders between sebum and comparator drugs (dapsone 7.5% gel, tretinoin 0.08% gel microspheres, tazarotene 0.1% foam, adapalene 0.3%/benzoyl peroxide 2.5% gel, and clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel), which have water-based or oil-in-water-based formulations, remained intact at 35 °C. When tested through differential scanning calorimetry (DSC), the melting point of topical minocycline foam 4% appeared to lower the melting temperature of model sebum below that of skin temperature [33.5 °C (92 °C) with topical minocycline foam 4% vs 39.6 °C (103°F) with an oil-in-water emulsion] [11].

Findings from an ex vivo study assessing the permeation and penetration of topical minocycline foam 4% through the skin showed that high minocycline concentrations were delivered to the epidermis and sebaceous appendage, and low concentrations to the dermis layer [11]. Following a single application of topical minocycline foam 4% (≈ 10 mg/cm^2) left to penetrate the skin for 12 h, 560 µg/mL and 17 µg/mL of minocycline entered the epidermal and dermal layers when the sebaceous appendages were left intact (calculated after accounting for average weight and density of skin, cellular volume corrections and volume of sebaceous appendages); after removal, 166 mg/mL and 25 µg/mL of minocycline entered the epidermal and dermal layers. Approximately half of delivered minocycline in the epidermis was found in the sebaceous appendages (3539 ng; 0.67% of applied dose) [11].

2.2 Antibacterial Activity

The exact mechanism of action of topical minocycline foam 4% in acne is currently unknown [10]. In an vitro study, topical minocycline foam 4% had potent antibacterial activity [12]. The minimal inhibitory concentration required to inhibit 90% of phenotypically- and genotypically-diverse *C. acnes* isolates (MIC_{90}) of topical minocycline foam 4% was 0.25 µg/mL (vs .5 µg/mL with minocycline powder), which was 4-fold lower than those of bacitracin and tetracycline, 8-fold lower than that of clindamycin, and ≥ 32-fold lower than those of the other assessed agents (including erythromycin, fusidic acid, muciprocin and neomycin) [12].

The favorable resistance profile of oral minocycline appears to be maintained with topical minocycline foam 4% [12]. The frequency of spontaneous resistance to topical minocycline foam 4% was low ($\leq 1 \times 10^{-8}$) in five strains of *C. acnes*, and cross-resistance occurred only with other tetracycline antibacterials and at minimal levels. Moreover, no second-step resistant mutant was seen with minocycline selection from 8 *C. acnes* strains studied, including those that were minocycline-resistant, and minocycline continued to have potent antibacterial activity against *C. acnes* over 15 serial passages [12].

2.3 Pharmacokinetic Properties

In a phase I study in patients aged 18–30 years with moderate to severe acne ($n = 30$), the systemic absorption of minocycline were minimal with once-daily topical minocycline foam 4% (maximum dose 4 g) applied over 21 days compared with a single dose of oral minocycline (≈ 1 mg/kg) [13]. The mean plasma concentration of minocycline over 24 h post-treatment (as assessed every 4 h) on days 1, 12 and 21 was ≈ 1 ng/mL with topical minocycline foam 4% and 100–1000 ng/mL with a single dose (≈ 1 mg/kg) of oral (extended-release) minocycline. The mean total exposure over 24 h post-treatment [area under the concentration-time curve (AUC_{24})] with topical minocycline foam 4% was substantially lower (≥ 479-fold) than the total minocycline exposure until the time of last detectable concentration (AUC_{tldc}) with oral minocycline (Table 1). The relative bioavailability of minocycline with topical minocycline foam 4% treatment relative to oral minocycline was ≈ 0.13% at days 12 and 21 [based on maximum plasma minocycline concentration (C_{max}) and AUC values]. Systemic accumulation, as assessed by AUC values, was very minimal with topical minocycline foam 4%, and minocycline plasma concentrations over 24 h post-application remained low at days 12 and 21 (Table 1). Steady-state pharmacokinetics with topical minocycline foam 4% were reached by day 6 [13].

In an open-label pediatric study, patients with moderate to severe acne ($n = 20$) experienced low systemic exposure to minocycline with once-daily application of topical minocycline foam 4% to the face, neck, upper chest, upper back, shoulder and upper arms over 7 days [10, 14]. While higher than those seen in adults (Table 1), mean C_{max} and AUC_{24} values were low after 7 days of treatment (4.5 ng/mL and 90.9 ng·h/mL in patients aged 10–11 years; 2.8 ng/mL and 54.0 ng·h/mL in patients aged 12–14 years; and 2.0 ng/mL and 40.8 ng·h/mL in patients aged 15 to < 17 years) [10].

Table 1 Mean pharmacokinetic parameters of topical minocycline foam 4% [13]

Treatment	C_{max} (ng/mL)	t_{max} (h)	AUC_{tldc} (ng·h/mL)	AUC_{24} (ng·h/mL)	$t_{½}$ (h)	AR[a]
Once-daily topical minocycline foam 4%						
Days 1–2 ($n = 30$)	1.7	11.5		31.8		
Days 12–13 ($n = 29$)	1.3	9.4		24.6		0.85
Days 21–25 ($n = 30$)	1.3	12.3		23.0		0.79
Oral minocycline (single dose; ≈ 1 mg/kg)						
Days 1–5 ($n = 30$)	873.4	2.7	15227.3		16.0	

AUC area under the concentration-time curve, AUC_{24} AUC from time 0 to 24 h, AUC_{tldc} AUC from time 0 to time of last detectable concentration, *AR* accumulation ratio, C_{max} maximum plasma concentration, $t_{½}$ terminal half-life, t_{max} time to maximum plasma concentration

[a] AUC_{24} relative to that of Day 1

3 Therapeutic Efficacy of Topical Minocycline Foam 4%

The therapeutic efficacy of topical minocycline foam 4% was assessed in three 12-week, randomized, vehicle-controlled phase III clinical studies: Study 22 [intent-to-treat (ITT) population $n = 1488$] [15], and two smaller studies that were identical in design [Studies 04 and 05 ($n = 466$ and 495)] [16]. Efficacy and tolerability (Sect. 4) findings from these studies are further supported by those from a dose-finding phase II trial [17], which is not discussed further.

In these trials [15, 16], eligible patients (aged ≥ 9 years) had moderate to severe facial acne as defined by an Investigator's Global Assessment (IGA) score of 3 or 4, 20–50 inflammatory lesions (including papules, pustules and nodules), 25–100 noninflammatory lesions (open and closed comedones) and ≤ 2 nodules. Patients with facial skin conditions (e.g. acne conglobate, acne fulminans or secondary acne) that may interfere with clinical evaluations were excluded from the studies. Study participants were prohibited from the uses of: oral [16] or systemic [15] retinoids or corticosteroids ≤ 12 weeks before randomization; topical retinoids, topical anti-inflammatory drugs and corticosteroids, oral antibacterials or other systemic acne treatments ≤ 4 weeks before randomization; and medicated facial cleansers or other topical acne mediations ≤ 1 week before randomization [15, 16].

Patients received topical minocycline foam 4% or a foam vehicle once daily for 12 weeks (self-treated at around the same time of day [15] or preferably in the evening [16]). At baseline, mean inflammatory and noninflammatory lesion counts ranged from 30.7–32.3 and 46.4–50.9 across the three studies [15, 16]. Most patients had moderate acne (i.e. IGA score 3; 83.1–91.4%); 8.6–16.9% of patients had severe acne (IGA score 4) [15, 16].

Eligible patients who completed Study 04 or 05 had the option of entering an open-label extension (Fig. 1), which was primarily a safety study (Sects. 3.2, 4) [18].

3.1 Short-Term Treatment

Twelve weeks' treatment with once-daily topical minocycline foam 4% was effective in improving both inflammatory and noninflammatory lesions of moderate to severe acne [15, 16]. In Studies 22 [15], 04 and 05 [16], the inflammatory lesion count was significantly improved from baseline

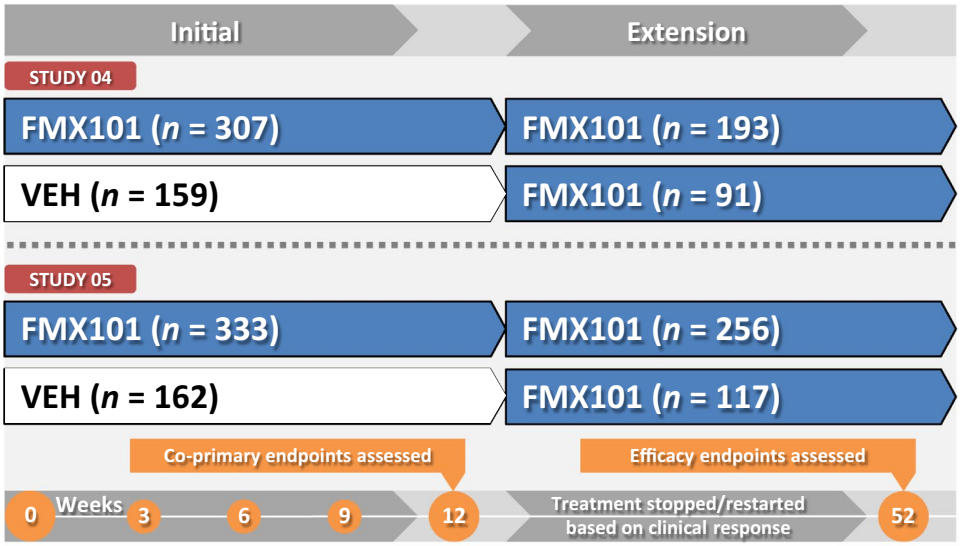

Fig. 1 Clinical trial design for Studies 04 and 05 [16] and their extension [18, 19]. Changes in inflammatory lesion count and IGA treatment success rates are reported in the animated figure (available online). *$p < 0.05$, **$p < 0.01$ vs vehicle. *FMX101* topical minocycline foam 4%, *IGA* Investigator's Global Assessment (score), *VEH* vehicle

at week 12 (co-primary endpoint), as well as at weeks 6 and 9 in Study 22, with topical minocycline foam 4% compared with vehicle (Table 2). Topical minocycline foam 4% significantly reduced the inflammatory lesion count from baseline at weeks 3, 6 and 9 (data not reported; $p \leq 0.001$ vs vehicle) as well as at week 12 [by 56% vs 43% with vehicle in Study 22, $p < 0.0001$ [15]; 44% vs 34% in Study 04 and 43% vs 34% in Study 05, $p \leq 0.01$ [16]]. In all studies, the noninflammatory lesion count at week 12 was also significantly improved from baseline with topical minocycline foam 4% relative to vehicle (Table 2) [15, 16]. In Study 22 [15], a steady decrease in noninflammatory lesion count with topical minocycline foam 4% was seen throughout the study, with significant reductions relative to vehicle seen at weeks 3 (data not reported; $p = 0.0005$) and 12 (39% vs 33% reduction; $p = 0.0036$), but not weeks 6 and 9.

In Studies 22 [15] and 05 [16], significant proportions of patients receiving topical minocycline foam 4% achieved IGA-assessed treatment success at week 12 (co-primary endpoint) (Table 2). Although this endpoint was not met in Study 04 (potentially due to an inadequate sample size), a post hoc analysis based on pooled data from Studies 04 and 05 showed that a significant proportion of topical minocycline foam 4% recipients achieved treatment success at week 12 relative to vehicle (Table 2) [16]. Findings from Study 22 showed significant rates of IGA-assessed treatment success with topical minocycline foam 4% compared with vehicle at weeks 6 and 9 (Table 2) [15].

Most patients in Studies 04 and 05 (74%) reported that they were either "satisfied" or "very satisfied" with topical minocycline foam 4%, according to pooled responses from a patient satisfaction questionnaire; this included questions pertaining to its ease of use, its comfort (feeling on the skin), and satisfaction compared with other previous treatments [16].

3.2 Longer-Term Treatment

Patients who had completed Study 04 or 05 with an IGA score that had not worsened compared with baseline were eligible to enter a 40-week, open-label extension study [18]. All patients ($n = 284$ and 373 from Studies 04 and 05) received once-daily topical minocycline foam 4% in the extension, and treatment was determined by clinical response; patients were allowed to stop treatment with the improvement or resolution of acne and to restart treatment with its worsening or recurrence. Concomitant acne medications were permitted throughout the extension [18].

Findings from the extension study indicated that topical minocycline foam 4% continued to be effective for a total of 52 weeks of treatment [18, 19]. In patients who received topical minocycline foam 4% in the 12-week studies, the inflammatory and noninflammatory lesion counts at week 52 had decreased from baseline (of the 12-week studies) by 64% and 53% in Study 04 patients (vs 72% and 70% in patients who initially received the foam vehicle) and 78% and 60% in Study 05 patients (vs 75% and 63%). In addition, 38% and 50% of patients receiving 52 weeks' treatment with topical minocycline foam 4% from Studies 04 and 05 achieved IGA-assessed treatment success at week 52 (vs 41% and 52% in those who initially received foam vehicle) [18, 19].

Most patients in the extension study (> 80%) reported that they were "satisfied" or "very satisfied" with topical minocycline foam 4% [18]. More than 85% of patients were "satisfied" or "very satisfied" with the drug's ease of use, and ≈ 80% of patients were "satisfied" or "very satisfied" with topical minocycline foam 4% compared with other previous treatments [18].

Table 2 Efficacy of topical minocycline foam 4% in phase III studies in patients aged ≥ 9 years with moderate to severe acne

Endpoint	Study 22 [15]		Study 04 [16]		Study 05 [16]		Studies 04 and 05[a] [16]	
	FMX101 (*n* = 738)	VEH (*n* = 750)	FMX101 (*n* = 307)	VEH (*n* = 159)	FMX101 (*n* = 333)	VEH (*n* = 162)	FMX101 (*n* = 640)	VEH (*n* = 321)
Absolute change from baseline								
Inflammatory lesion count at week 6	− 13.1***	− 9.6						
Inflammatory lesion count at week 9	− 15.6***	− 11.7						
Inflammatory lesion count at week 12[b]	− 16.9***	− 13.4	− 14.1**	− 11.2	− 13.5**	− 10.7	− 13.8***	− 10.9
Noninflammatory lesion count at week 12	− 18.8*	− 15.9	− 16.5**	− 10.3	− 13.2*	− 7.0	− 14.8**	− 8.6
Rate of IGA treatment success[c] (RR) [%]								
Week 6	11.6** (1.8)	6.5						
Week 9	20.5*** (1.8)	11.7						
Week 12[b]	30.8*** (1.6)	19.6	8.1 (1.7)	4.8	14.7* (1.9)	7.9	11.5* (1.8)	6.3

FMX101 topical minocycline 4%, *IGA* Investigator's Global Assessment, *LSM* least squares mean, *RR* risk ratio, *VEH* vehicle

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$ vs VEH

[a]Data from post hoc pooled analyses

[b]Co-primary endpoint

[c]Defined as an IGA score of 0 (clear skin) or 1 (rare noninflammatory lesions) in addition to a ≥ 2-grade improvement from baseline

4 Tolerability of Topical Minocycline Foam 4%

Once-daily topical minocycline foam 4% was generally well tolerated in phase III clinical trials [15, 16, 18]. In Studies 04 and 05, safety assessments were conducted at weeks 3, 6, 9 and 12 [15, 16]. After 12 weeks, treatment-emergent adverse events (TEAEs) occurred in 26.2% and 24.5% of topical minocycline foam 4% and foam vehicle recipients in Study 22 [15], 16.9% and 18.2% of patients in Study 04 [16], and 33.0% and 26.5% of patients in Study 05 [16]; most of these TEAEs were considered to be mild to moderate in severity [15, 16]. In Study 22, all TEAEs were transient and resolved during the study [15].

Treatment-related adverse events (TRAEs) occurred in a minority of patients receiving topical minocycline foam 4% (2.0–3.8%) and foam vehicle recipients (1.9–4.0%) in Study 22 [15] and Studies 04 and 05 [15, 16]; none were considered to be treatment-related. The most common TRAE in Study 22 was increased creatinine phosphokinase levels (1.2% vs 0.3% of patients in the respective groups) [15]. Four (0.5%) and three (0.4%) patients from the topical minocycline foam 4% and vehicle groups in Study 22 discontinued treatment on account of TRAEs [causative adverse events (AEs) not specified] [15]. SAEs occurred in 1 topical minocycline foam 4% recipient (vs 3 vehicle recipients) in Study 22 [15], 1 (vs 0) in Study 04, and 4 (vs 2) in Study 05 [16]; none were considered to be treatment-related [15, 16].

The tolerability profile of topical minocycline foam 4% over 52 weeks was consistent with that seen in the 12-week trials [18]. The overall incidences of TEAEs were similar to those from the shorter-term trials (22.9% and 32.2% in patients originally from Study 04 and 05 over 52 weeks). TRAEs were few and mild to moderate in severity (not reported). Discontinuations due to TEAEs were reported in seven patients in the extension study; three TEAEs leading to discontinuations were considered to be probably (application-site dermatitis) or possibly (application-site edema and acne) related to treatment, but not serious. None of the three SAEs reported (pneumonia, fatigue, head injury from fainting) were considered treatment-related or led to discontinuation [18].

Findings from a subanalysis of data from the three 12-week studies indicated that once-daily topical minocycline foam 4% was similarly well tolerated in pediatric patients ($n = 67$, 604 and 706 in patients aged 9–12, 13–17 and ≥ 18 years, respectively), with no serious TRAEs reported [14]. TEAEs occurred at similar incidences among the different age groups (26.9% vs 19.6% in topical minocycline foam 4% and vehicle recipients aged 9–12 years; 26.2% vs 24.0% in patients aged 13–17 years; and 25.9% vs 25.3% in patients aged ≥ 18 years) [14].

4.1 Dermal Safety

Cutaneous TRAEs with once-daily topical minocycline foam 4% in phase III studies were not common. In Study 22,

these included acne (3.0% vs 3.5% in topical minocycline foam 4% and vehicle recipients), yellow skin (0.4% vs 0.7%), dry skin, pruritus and skin discoloration (each occurring in 0.3% for both groups), and facial swelling (0.1% vs 0.0%) [15]. In Studies 04 and 05, cutaneous TRAEs included application site discoloration (5 patients across both studies), application site discomfort (1 patient from Study 04) and yellowing of nails (3 patients across both studies) [16]. In the Study 04 and 05 extension study, application-site TEAEs included acne (1.1% and 0% of patients originally from Studies 04 and 05), and rash, cyst and dry skin (numerical data not reported); > 95% of patients experienced either mild facial TEAEs (specified as erythema, dryness, hyperpigmentation, skin peeling or facial itching) or none at all [18].

The dermal safety of topical minocycline foam 4% was further investigated in healthy volunteers (aged ≥ 18 years) in four phase I studies specifically assessing for the potential of phototoxicity, photoallergy, skin sensitization and cumulative skin irritation ($n = 32$–233) [20]. These studies found no evidence of clinically relevant phototoxicity, photoallergy, sensitization and skin irritation potential with topical minocycline foam 4% treatment. TEAEs occurred in a total of 21 participants across the four studies; however, none were considered to be treatment-related or serious [20].

5 Dosage and Administration of Topical Minocycline Foam 4%

Topical minocycline foam 4% is approved in the USA for the treatment of inflammatory lesions of non-nodular, moderate to severe acne in adults and pediatric patients aged ≥ 9 years [10]. It is for topical use only and should not be used orally, ophthalmically or intravaginally. After shaking the can well, a small amount (e.g. a cherry-sized amount) of foam should be dispensed from the can onto the fingertips and then rubbed into acne-affected parts of the face; additional amounts should also be applied to other affected areas (neck, shoulders, arms, back or chest). The foam should be applied [at around the same time each day (≥ 1 h before bedtime)] as required for all acne-affected parts of the skin to be treated; the patient should not bathe, shower or swim for ≥ 1 h after application. The safety and effectiveness of topical minocycline foam 4% has not been established in patients aged < 9 years [10].

Although topical minocycline foam 4% did not induce phototoxicity or photoallergic responses in human dermal safety studies (Sect. 4.1), patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while undergoing treatment [10]. If patients need to be outdoors while using topical minocycline foam 4%, they should wear loose-fitting clothes that protect the skin from sun exposure and discuss other sun protection measures with their physician. Treatment should be discontinued at the first evidence of sunburn [10]. Local prescribing information should be consulted for detailed information regarding drug interactions, special warnings and other precautions.

6 Current Status of Topical Minocycline Foam 4% in Acne Vulgaris

Selecting the most appropriate option among the many treatments available for acne depends on a number of patient-related factors [1]. In addition to the severity, site and extent of acne, there are considerations such as concomitant therapies, comorbidities, and the preferences of the patient (and therefore the likelihood of treatment adherence). The American Academy of Dermatology (AAD) guidelines [1, 21] recommend targeting multiple facets of acne pathogenesis (Sect. 1) with combination treatment; while benzoyl peroxide and topical retinoids may be used as monotherapy for mild acne, they are typically used with a topical antibacterial (e.g. erythromycin, clindamycin), particularly for moderate to severe acne [1].

Monotherapy with antibacterials is usually not recommended due to the risk of developing antibacterial resistance [1]. Although oral antibacterials have long been a mainstay of acne treatment, the risk of systemic AEs is another major concern for their use and limits their therapeutic potential. Tetracyclines (including tetracycline, minocycline and doxycycline) have lower bacterial resistance rates and are the preferred first-line option for acne among oral antibacterials [1]. Extended-release formulations of oral minocycline have also been developed to reduce overall exposure and therefore minimize AEs [22, 23]. Other, non-antibacterial topical agents may also be limited in their use due to their associated adverse effects, such as concentration-dependent skin irritation with benzoyl peroxide and skin irritation and peeling with retinoids [1].

Topical minocycline foam 4% is the first topical minocycline product and was formulated to provide a long-term, low-risk treatment option for moderate to severe acne (Sect. 2). In contrast to water-based topical agents, the high lipid content of topical minocycline foam 4% allows the drug to be delivered efficiently through sebum to the affected pilosebaceous units without markedly penetrating into the dermis (Sect. 2.1). Topical minocycline foam 4% demonstrated potent in vitro antibacterial activity against *C. acnes* isolates and low rates of bacterial resistance (Sect. 2). Because there is minimal systemic absorption and accumulation of minocycline with topical minocycline foam 4%, the risk for antibacterial-related systemic toxicity is substantially reduced; although minocycline exposure from topical

minocycline foam 4% appeared to be higher in younger patients in pharmacokinetic studies, it was minimal in all assessed patient groups (Sect. 2.3).

In phase III clinical trials, once-daily topical minocycline foam 4% significantly improved moderate to severe acne in pediatric and adult patients (Sect. 3). During 12 weeks' treatment, reductions were seen in both inflammatory and noninflammatory lesions and significant proportions of patients in all trials achieved IGA treatment success (Sect. 3.1). Topical minocycline foam 4% continued to be effective in treating acne for a total of 52 weeks of treatment in patients who participated in the Study 04 or 05 extension (Sect. 3.2). In both shorter- and longer-term studies, most patients were satisfied or highly satisfied with topical minocycline foam 4%, including in terms of its ease of use and in comparison to other previous treatments (Sects. 3.1, 3.2).

Topical minocycline foam 4% was also generally well tolerated during up to 52 weeks in clinical studies, with most TEAEs and all SAEs considered to be unrelated to treatment (Sect. 4). Findings from a subanalysis demonstrated topical minocycline foam 4% to have a similar tolerability profile in pediatric patients (Sect. 4). Cutaneous TRAEs were not common and, in most patients, facial TEAEs were mild or absent (Sect. 4.1). In healthy volunteers, topical minocycline foam 4% did not produce any clinically significant effects relating to phototoxicity, photoallergy, skin sensitization and skin irritation (Sect. 4.1), all of which are potential side effects of oral antibacterials and/or other topical agents [1].

While topical minocycline foam 4% was well-tolerated and reportedly more satisfactory to use than other acne treatments (Sect. 3), direct head-to-head trials with frequently used treatments (e.g. oral minocycline) would be useful in more definitively determining the place of topical minocycline foam 4% in the management of moderate to severe acne. Because patients in the open-label extension for Studies 04 and 05 were permitted to use concomitant acne medications (Sect. 3.2), longer-term data on the sole use of topical minocycline foam 4% to treat acne would be beneficial in establishing its long-term efficacy, particularly given that acne often requires long-term treatment. Cost-effectiveness studies and longer-term real-world data outside of clinical trials would also be valuable in establishing its long-term suitability.

In conclusion, topical minocycline foam 4% was effective and well-tolerated when used for the treatment of moderate to severe acne in patients aged ≥ 9 years. Although further evidence will be helpful in more definitively establishing its place in acne management, current evidence indicates that topical minocycline foam 4% is a useful addition to available treatment options for the management of inflammatory lesions of non-nodular, moderate to severe acne in adult and pediatric patients aged ≥ 9 years.

Data Selection Topical Minocycline Foam 4%: 50 records identified

Duplicates removed	5
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	2
Excluded during writing (e.g. reviews; duplicate data;small patient number; nonrandomized/phase I/II trials)	20
Cited efficacy/tolerability articles	7
Cited articles not efficacy/tolerability	16

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Amzeeq, topical minocycline foam, acne vulgaris. Records were limited to those in English language. Searches last updated 16 April 2020

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Compliance with Ethical Standards

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Conflict of interest Julia Paik is a salaried employee of Adis International Ltd/Springer Nature, is responsible for the article content and declares no relevant conflicts of interest.

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