AMZEEQ- minocycline aerosol, foam
VYNE Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMZEEQ safely and effectively. See full prescribing information for AMZEEQ.

AMZEEQ® (minocycline) topical foam
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

AMZEEQ is a tetracycline-class drug indicated to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. (1)

Limitations of Use
This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated. (5.14)

DOSAGE AND ADMINISTRATION

Apply AMZEEQ to affected areas once daily. AMZEEQ should be gently rubbed into the skin. (2)

DOSAGE FORMS AND STRENGTHS

Foam, 4% (3)

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any of the ingredients within AMZEEQ. (4)

WARNINGS AND PRECAUTIONS

- The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. (5.1)
- The use of tetracycline-class of drugs orally during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth. (5.2, 5.3, 5.4, 8.1, 8.4)
- If *Clostridioides difficile* associated diarrhea occurs, discontinue AMZEEQ. (5.5)
- If liver injury is suspected, discontinue AMZEEQ. (5.6)
- If renal impairment exists, oral minocycline doses may need to be adjusted to avoid excessive systemic accumulations of the drug and possible liver toxicity. (5.7)
- Oral minocycline may cause central nervous system side effects including lightheadedness, dizziness, or vertigo. (5.8)
- Oral minocycline may cause intracranial hypertension in adults and adolescents. Discontinue AMZEEQ if symptoms occur. (5.9)
- Oral minocycline has been associated with autoimmune syndromes; discontinue AMZEEQ immediately if symptoms occur. (5.10)
- Photosensitivity can occur with oral tetracycline. Patients should minimize or avoid exposure to natural or artificial sunlight. (5.11)
- Oral minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue AMZEEQ immediately if symptoms occur. (5.12)

ADVERSE REACTIONS

The most commonly observed adverse reaction is headache. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact VYNE Pharmaceuticals Inc. at 1-844-375-3673 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. (7.1)
- Penicillin: avoid coadministration. (7.2)

USE IN SPECIFIC POPULATIONS

- Minocycline like other tetracycline-class drugs can cause fetal harm when administered orally to a

pregnant woman. (5.2, 8.1)
- The use of drugs of the tetracycline class orally during tooth development may cause permanent discoloration of teeth. (5.3, 8.2, 8.4)
- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AMZEEQ is indicated for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older [*see Clinical Studies (14)*].

Limitations of Use

This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated [*see Warnings and Precautions (5.14)*].

2 DOSAGE AND ADMINISTRATION

For topical use only, not for oral, ophthalmic or intravaginal use [*see Clinical Studies (14)*].

After shaking the can well, a small amount of topical foam (e.g. a cherry-sized amount) should be expressed from the can onto the fingertips of the hand and then rubbed into acne-affected parts of the face. This should be repeated as needed until all acne-affected parts of the face are treated. If acne is present on other parts of the patient’s body (neck, shoulders, arms, back or chest), additional amounts of topical foam should also be applied to these areas. The topical foam should be applied at approximately the same time each day at least 1 hour before bedtime. The patient should not bathe, shower or swim for at least 1 hour after application of the product.

3 DOSAGE FORMS AND STRENGTHS

Topical foam, 4%

Each gram of AMZEEQ contains 40 mg of minocycline equivalent to 43 mg of minocycline hydrochloride and is supplied as a yellow suspension in a pressurized aluminum aerosol container (can).

4 CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within AMZEEQ.

5 WARNINGS AND PRECAUTIONS

5.1 Flammability

The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).

5.2 Teratogenic Effects

Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13)]*.

5.3 Tooth Discoloration

The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development.

The safety and effectiveness of AMZEEQ have not been established in pediatric patients less than 9 years of age.

5.4 Inhibition of Bone Growth

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. The safety and effectiveness of AMZEEQ have not been established in patients less than 9 years of age *[see Use in Specific Populations (8.1, 8.4)].*

Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated orally early in pregnancy *[see Use in Specific Populations (8.1)].*

5.5 *Clostridioides difficile* Associated Diarrhea

Clostridioides difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD.

Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.6 Hepatotoxicity

Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use in the treatment of acne.

5.7 Metabolic Effects

The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.

5.8 Central Nervous System Effects

Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.

5.9 Intracranial Hypertension

Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concomitant use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension.

Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.

5.10 Autoimmune Syndromes

Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including AMZEEQ.

5.11 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although AMZEEQ did not induce phototoxicity or photoallergic responses in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using minocycline. If patients need to be outdoors while using AMZEEQ, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.

5.12 Serious Skin/Hypersensitivity Reaction

Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with oral minocycline use in patients with acne. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue AMZEEQ immediately.

5.13 Tissue Hyperpigmentation

Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.

5.14 Development of Drug-Resistant Bacteria

AMZEEQ has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using AMZEEQ, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of AMZEEQ, it should be used only as indicated.

5.15 Superinfection/Potential for Microbial Overgrowth

Use of AMZEEQ may result in overgrowth of non-susceptible organisms, including fungi.

If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In 3 randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied AMZEEQ or vehicle once daily for 12 weeks. A total of 1,356 subjects were treated with AMZEEQ and 1,058 with vehicle. The majority of subjects were White (74%) and female (60%). Approximately 34% were Hispanic/Latino and 49% were younger than 18 years of age.

The most common adverse reaction reported by ≥1% of subjects treated with AMZEEQ and more frequently than in subjects treated with vehicle was headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle.

Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. Table 1 presents the active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ.

Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ.

Table 1: Facial Cutaneous Tolerability Assessment

Symptom/Severity	AMZEEQ, % (N=1,377)		
	Mild	Moderate	Severe
Erythema	14.2	1.5	0
Dryness	6.8	0.6	0
Hyperpigmentation*	12.4	2.8	0.1
Skin Peeling	3.2	0.2	0
Itching	5.1	0.8	0.1

* Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne.

In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

7 DRUG INTERACTIONS

7.1 Anticoagulants

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

7.2 Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

7.3 Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with AMZEEQ use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of AMZEEQ in humans is low following once daily topical administration of AMZEEQ for 21 days *[see Clinical Pharmacology (12.3)]*. Because of low systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug.

Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy *[see Warnings and Precautions (5.2, 5.3, 5.4)* and *Use in Specific Populations (8.4)]*.

Animal reproduction studies were not conducted with AMZEEQ. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during the period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus [*see Warnings and Precautions (5.2)*].

Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (750 and 500 times, respectively, the

systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (250 times the systemic exposure at the MRHD based on AUC comparison).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (650 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

8.2 Lactation

Risk Summary

Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with AMZEEQ *[see Warnings and Precautions (5.2)].*

8.4 Pediatric Use

The safety and effectiveness of AMZEEQ have been established in pediatric patients 9 years of age and older for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. Use of AMZEEQ for this indication is supported by three adequate and well controlled 12-week trials in patients 9 years of age and older; two of the trials included a 40-week open-label extension. Additional data was obtained from a 7-day open-label safety and pharmacokinetics study conducted in 20 patients 10 years to less than 17 years of age with acne vulgaris *[see Clinical Pharmacology (12.3)* and *Clinical Studies (14)]*. A total of 686 subjects 9 years of age and older received AMZEEQ in these clinical trials.

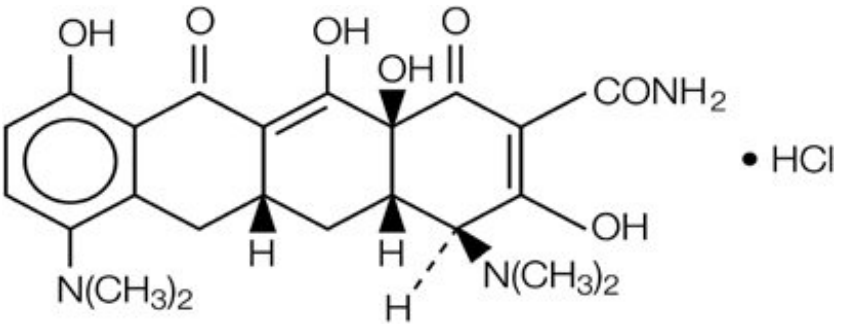
Safety and effectiveness for this indication have not been established in pediatric patients less than 9 years of age. The use of oral tetracycline drugs during tooth development below the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and inhibition of bone growth *[see Warnings and Precautions (5.2, 5.3)]*.

8.5 Geriatric Use

Clinical studies of AMZEEQ did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

Minocycline hydrochloride, a semi-synthetic derivative of tetracycline, is [4S-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a- tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride. The structural formula is represented below:



$C_{23}H_{27}N_3O_7 \bullet HCl$ M. W. 493.94

Each gram of AMZEEQ contains micronized minocycline 40 mg equivalent to 43 mg minocycline hydrochloride in a yellow suspension foam.

In addition, the 4% AMZEEQ topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol. AMZEEQ topical foam is dispensed from an aluminum container (can) pressurized with propellant (butane + isobutane + propane).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of AMZEEQ for the treatment of acne is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of AMZEEQ for the treatment of acne are unknown.

12.3 Pharmacokinetics

In a pharmacokinetic study, male and female subjects 18 years of age or older with acne vulgaris (N=30) applied approximately 4 grams of AMZEEQ topically to the face, neck, upper chest, upper back, shoulder and upper arms once daily for 21 days. The mean ± SD C_{max} and $AUC_{0\text{-}24h}$ were 1.3 ± 0.6 ng/mL and 23.0 ± 10.8 ng·h/mL, respectively at Day 21 for AMZEEQ. After daily application of AMZEEQ in subjects with acne for 21 days, steady-state was reached by Day 6 and systemic accumulation of minocycline was not evident.

<u>Specific Populations</u>

Age: Pediatric Population

Pharmacokinetics of minocycline was evaluated in 20 subjects 10 years to less than 17

years of age with acne vulgaris following application of approximately 4 grams of AMZEEQ topically to the face, neck, upper chest, upper back, shoulder and upper arms once daily for 7 days. Minocycline was detected in all samples obtained on Day 7. Pharmacokinetic results are presented by age group in Table 2. The overall pediatric population showed 2.4-fold and 2.7-fold higher C_{max} and $AUC_{0\text{-}24h}$ compared to the adult population.

Table 2: Clinical Pharmacokinetics of Minocycline when treated with AMZEEQ (~4 g) in Pediatric Subjects Aged 10 to <17 years with Acne Vulgaris

Age Group (years)	Mean ± SD C_{max} (ng/mL)	Mean ± SD $AUC_{0\text{-}24h}$ (ng·h/mL)
10 - 11	4.5 ± 4.0	90.9 ± 90.2
12 - 14	2.8 ± 2.2	54.0 ± 46.2
15 - <17	2.0 ± 1.2	40.8 ± 23.8
10 - <17	3.1 ± 2.7	61.1 ± 59.2

12.4 Microbiology

Resistance

Propionibacterium acnes strains displayed a low propensity for the development of resistance to minocycline, with spontaneous mutation frequencies being $<10^{-8}$ at 2 to 16 × MIC.

Antimicrobial Activity

Minocycline is active in vitro against most isolates of *Propionibacterium acnes*; however, the clinical significance is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated in both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females.

Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (10,000 times the systemic exposure at the MRHD

based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (3,800 or 10,000 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis.

Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

14 CLINICAL STUDIES

The safety and efficacy of AMZEEQ was assessed in three 12-week, multicenter, randomized, double-blind, vehicle-controlled studies (Study 1 [NCT02815267], Study 2 [NCT02815280], and Study 3 [NCT03271021]) in subjects with moderate to severe acne vulgaris. Efficacy was assessed in a total of 2,418 subjects 9 years of age and older. AMZEEQ or its vehicle were applied once daily for 12 weeks; no other topical or systemic medication affecting the course of acne vulgaris was permitted for use during these studies.

Subjects were required to have an inflammatory and non-inflammatory lesion count in the range 20-50 lesions and 25-100 lesions respectively, and an Investigator Global Assessment (IGA) score of 3 (“moderate”) or 4 (“severe”) at baseline.

Overall, 74% were Caucasian and 61% were female. Forty-two (2%) subjects were 9 to 11 years of age, 1,139 (47%) subjects were 12 to 17 years of age, and 1,237 (51%) subjects were 18 years or older. At baseline, subjects had a mean inflammatory lesion count of 31.2 and a mean non-inflammatory lesion count of 49.3. Additionally, approximately 85% of subjects had an IGA score of 3 (“moderate”).

The co-primary efficacy endpoints were the absolute change from baseline in inflammatory lesion counts at Week 12 and the proportion of subjects with treatment success at Week 12, defined as an IGA score of 0 (“clear”) or 1 (“almost clear”), and at least a two-grade improvement (decrease) from baseline at Week 12. The efficacy results are presented in Table 3.

Table 3: Clinical Efficacy of AMZEEQ in Subjects with Acne Vulgaris at Week 12

	Study 1		**Study 2**		**Study 3**	
	AMZEEQ (N=307)	**Vehicle (N=159)**	**AMZEEQ (N=312)**	**Vehicle (N=152)**	**AMZEEQ (N=738)**	**Vehicle (N=750)**
IGA						
Treatment Success[a]	8.1%	4.8%	15.8%	8.4%	30.8%	19.6%
Difference from Vehicle (95% CI)	3.3% (-1.5%, 8.2%)		7.4% (0%, 13.7%)		11.2% (6.6%, 15.8%)	
Inflammatory Lesion Count						
Mean[b] Absolute Change from Baseline	-14.0	-11.2	-13.7	-10.5	-16.4	-12.7

Difference from Vehicle (95% CI)	-2.8 (-4.9, -0.7)	-3.2 (-5.6, -0.9)	-3.7 (-4.8, -2.5)
Mean[b] Percent Change from Baseline	-44% -34%	-43% -34%	-54% -42%
Difference from Vehicle (95% CI)	-10% (-17%, -3%)	-10% (-17%, -2%)	-12% (-16%, -8%)

[a] Treatment success is defined as an IGA score of 0 (“clear”) or 1 (“almost clear”), and at least a two-grade improvement (decrease) from baseline.
[b] Means presented in table are Least Square (LS) means.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AMZEEQ® (minocycline) topical foam, 4% is a yellow suspension supplied in a pressurized aluminum aerosol container (can). Each gram of AMZEEQ contains 40 mg of minocycline equivalent to 43 mg of minocycline hydrochloride, and is supplied as follows:

NDC 72356-101-03 30 g Can

Storage

AMZEEQ must be stored at 2ºC - 8ºC (36ºF - 46ºF) until dispensed to the patient.

Once dispensed, the patient is to store AMZEEQ at room temperature below 25ºC (77ºF) for 90 days. Do not store in the refrigerator.

Handling

Allow the can to warm to room temperature before first use.

Shake can well before use.

WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49ºC (120ºF).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Inform patients using AMZEEQ (minocycline) topical foam, 4% of the following information and instructions:

Flammability

The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

Tooth Discoloration

Advise caregivers of pediatric patients that AMZEEQ may cause permanent discoloration of deciduous and permanent teeth during tooth development (generally up to the age of 8 years) based on observations with oral tetracycline.

Lactation

Advise women that breastfeeding is not recommended during AMZEEQ therapy.

Tissue Hyperpigmentation

Inform patients that AMZEEQ may cause discoloration of skin, scars, teeth or gums based on observations with oral minocycline.

Clostridioides difficile Associated Diarrhea

Advise patients that *Clostridioides difficile* associated diarrhea can occur with oral minocycline therapy. Advise patients to seek medical attention if they develop watery or bloody stools while using AMZEEQ.

Hepatotoxicity

Inform patients about the possibility of hepatotoxicity reported with oral minocycline. Advise patients to seek medical advice if they experience symptoms or signs of hepatotoxicity, including loss of appetite, tiredness, diarrhea, jaundice, increased bleeding tendencies, confusion, and sleepiness.

Central Nervous System Effects

Inform patients that central nervous system adverse reactions including dizziness or vertigo have been reported with oral minocycline therapy. Caution patients about driving vehicles or using hazardous machinery if they experience such symptoms while on AMZEEQ.

Intracranial Hypertension

Inform patients that intracranial hypertension can occur with minocycline therapy. Advise patients to seek medical attention if they develop unusual headache, visual symptoms, such as blurred vision, diplopia, and vision loss.

Photosensitivity

Inform patients that photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines, including minocycline. Advise patients to minimize or avoid exposure to natural or artificial UV light (tanning beds or UVA/B treatment) while using AMZEEQ. Discuss other sun protection measures, if patients need to be outdoors while using AMZEEQ. Advise patients to discontinue treatment at the first evidence of sunburn.

Autoimmune Syndromes

Inform patients that autoimmune syndromes, including drug-induced lupus-like syndrome, autoimmune hepatitis, vasculitis and serum sickness have been observed with oral tetracycline-class drugs, including minocycline. Symptoms may be manifested by arthralgia, fever, rash and malaise. Advise patients who experience such symptoms to stop the drug immediately and seek medical help.

Other Information

AMZEEQ should be applied exactly as directed.

AMZEEQ may stain fabric.

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Manufactured for: VYNE Pharmaceuticals Inc., Bridgewater, NJ 08807
Product of Portugal or Switzerland

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PATIENT INFORMATION
AMZEEQ® (am-Zeek)
(minocycline)
topical foam

Important Information: AMZEEQ is for use on skin only (topical use). AMZEEQ is not for use in your mouth, eyes or vagina.

What is AMZEEQ?
AMZEEQ is a prescription medicine used on the skin (topical) for the treatment of pimples and red bumps (non-nodular inflammatory lesions) that happen with moderate to severe acne vulgaris in adults and children 9 years of age and older.
AMZEEQ should not be used for the treatment of infections.
It is not known if AMZEEQ is safe and effective in children under 9 years of age.

Do not use AMZEEQ if you are allergic to any tetracycline medicines or to any of the ingredients in AMZEEQ. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

What should I tell my healthcare provider before using AMZEEQ?
Before using AMZEEQ, tell your healthcare provider about all of your medical conditions, including if you:

- have diarrhea or watery stools
- have liver problems
- have kidney problems
- are pregnant or plan to become pregnant. Taking tetracycline medicines by mouth during pregnancy may cause serious side effects on the growth of bone and teeth of your baby. AMZEEQ topical foam is used on your skin and it is not known if it will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Do not breastfeed during treatment with AMZEEQ.

Tell your healthcare provider about all the other medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Tetracycline medicines taken by mouth may affect the way other medicines work, and may increase your risk of certain side effects.
Especially tell your healthcare provider if you take:

- a blood thinner medicine.
- a penicillin antibiotic medicine
- isotretinoin

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How should I use AMZEEQ?

- See the detailed **"Instructions for Use"** included with this leaflet for directions about how to apply AMZEEQ the right way.
- Use AMZEEQ exactly as your healthcare provider tells you.
- Apply AMZEEQ to the affected skin area(s) at about the same time each day, at least 1 hour before bedtime.
- Do not bathe, shower, or swim for at least 1 hour after applying AMZEEQ.
- Wash your hands after applying AMZEEQ.

What should I avoid while using AMZEEQ?

- AMZEEQ is flammable. Avoid fire, flame, and smoking when applying and right after you apply AMZEEQ.
- Limit your time in sunlight. Avoid sunlight or artificial sunlight such as sunlamps or tanning beds. Use sun protection measures such as sunscreen and wear loose-fitting clothes that cover your skin while out in sunlight. Stop using AMZEEQ if you get sunburn.
- Minocycline taken by mouth may cause feelings of light-headedness, dizziness, or spinning (vertigo). You should not drive or operate dangerous machinery if you have these symptoms during treatment with AMZEEQ.

What are possible side effects of AMZEEQ?
AMZEEQ contains minocycline, a tetracycline medicine. Tetracyclines, when taken by mouth, may cause serious side effects, including:

- **Harm to an unborn baby.** See **"What should I tell my healthcare provider before using AMZEEQ?"**
- **Permanent tooth discoloration.** Tetracycline medicine when taken by mouth may permanently turn a baby or child's teeth yellow-gray-brown during tooth development. You should not use AMZEEQ during tooth development. Tooth development happens in the second and third trimesters of pregnancy, and from birth up to 8 years of age.
- **Slow bone growth.** Tetracycline medicine taken by mouth may slow bone growth in infants and children.Slow bone growth is reversible after stopping treatment.
- **Diarrhea.** Diarrhea can happen with most antibiotics, including minocycline taken by mouth. This diarrhea may be caused by an infection (*Clostridioides difficile)* in your intestines. Call your healthcare provider right away if you get watery or bloody stools while using AMZEEQ.
- **Liver problems.** Minocycline taken by mouth to treatacne can cause serious liver problems that may lead to death. Stop using AMZEEQ and call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:

  - loss of appetite
  - tiredness
  - diarrhea
  - bleeding more easily than normal
  - confusion
  - sleepiness

- yellowing of your skin or the white of your eyes (jaundice)

- **Central nervous system effects.** See "**What should I avoid while using AMZEEQ?**"
- **Increased pressure in the brain (intracranial hypertension)**. This condition may lead to vision changes and permanent vision loss. You are more likely to get intracranial hypertension if you are a female of childbearing potential and are overweight or have a history of intracranial hypertension. Stop using AMZEEQ and tell your healthcare provider right away if you have blurred vision, double vision, vision loss, or unusual headaches.
- **Immune system reactions including a lupus-like syndrome, hepatitis, and inflammation of blood or lymph vessels (vasculitis)** have happened during treatment with minocycline taken by mouth**.** Call your healthcare provider right away if you get a fever, rash, joint pain, or body weakness.
- **Sensitivity to sunlight (photosensitivity).** See **"What should I avoid while using AMZEEQ?"**
- **Serious skin or allergic reactions** have happened during treatment with minocycline taken by mouth that may affect parts of your body such as your liver, lungs, kidneys and heart. Sometimes these can lead to death. Stop using AMZEEQ and go to the nearest hospital emergency room right away if you have any of the following signs or symptoms:

  - skin rash, hives, sores in your mouth, or your skin blisters and peels
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble swallowing or breathing
  - blood in your urine
  - fever, yellowing of the skin or the whites of your eyes (jaundice), dark colored urine
  - pain on the right side of the stomach area (abdominal pain)
  - chest pain or abnormal heartbeats
  - swelling in your legs, ankles, and feet

- **Discoloration (hyperpigmentation).** Minocycline taken by mouth may cause darkening of your skin, scars, teeth, or gums.

The most common side effect of AMZEEQ is headache.
Your healthcare provider may stop your treatment with AMZEEQ if you develop certain side effects.
These are not all the possible side effects with AMZEEQ.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMZEEQ?

- Store AMZEEQ at room temperature below 77ºF (25ºC) for 90 days.
- Do not store AMZEEQ in the refrigerator.
- Do not puncture or burn the AMZEEQ can.
- Do not expose to heat or temperatures above 120ºF (49ºC)

Keep AMZEEQ and all medicines out of the reach of children.

General information about the safe and effective use of AMZEEQ.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AMZEEQ for a condition for which it was not prescribed. Do not give AMZEEQ to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about AMZEEQ that is written for health professionals.

What are the ingredients in AMZEEQ?
Active ingredient: minocycline
Inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol and propellant (butane + isobutane + propane).

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For more information, go to www.AMZEEQ.com or call VYNE Pharmaceuticals Inc. at 1-844-375-3673.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 01/2021

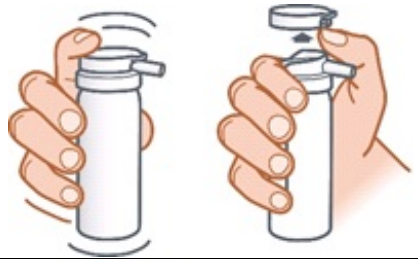
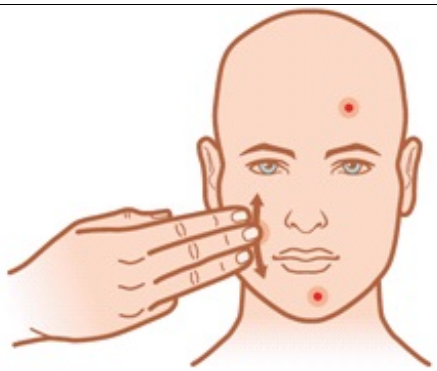
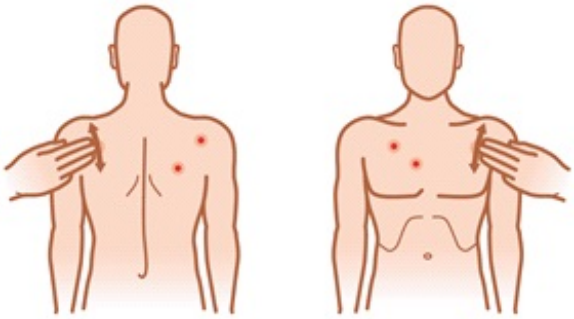
INSTRUCTIONS FOR USE
AMZEEQ® (am-Zeek)
(minocycline)
topical foam

Important Information: AMZEEQ is for use on skin only (topical use). AMZEEQ is not for use in your mouth, eyes or vagina.

Read this Instructions for Use before you start using AMZEEQ and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. Use AMZEEQ exactly as your healthcare provider tells you.

Before applying AMZEEQ:

- Allow the AMZEEQ can to warm to room temperature before first use.
- Wash your face gently with mild cleanser, rinse with water, and pat your skin dry.

	**Step 1:** Shake the can well. Place thumb under tab above nozzle and lift up to remove the cap from the AMZEEQ foam can.
	Step 2: Press the top of the can to dispense a small amount of AMZEEQ foam onto your fingertips.
	**Step 3:** Apply and gently rub AMZEEQ foam into the affected areas.
	**Step 4:** If acne is present on other parts of your body (neck, shoulders, arms, back or chest), additional amounts of AMZEEQ foam should also be applied to these affected areas as directed by your healthcare provider.
• Wash your hands after applying AMZEEQ. • AMZEEQ can stain fabric.	

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 01/2021

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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

AMZEEQ Trade Labels for Country-of-Origin Portugal

NDC 72356-101-03

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

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To report SUSPECTED ADVERSE REACTIONS, contact VYNE Pharmaceuticals at 1-844-375-3673 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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NDC 72356-**101**-03

amzeeq®
(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

VYNE™ THERAPEUTICS

30 g

Must be refrigerated, store at 2°C to 8°C (36°F to 46°F) until dispensed to the patient.
Once dispensed, the patient is to store AMZEEQ at room temperature below 25°C (77°F) for 90 days.
Do not store in the refrigerator.
Allow the can to warm to room temperature before first use.
Shake can well before use.

Date received from pharmacy / /
Discard unused portion 90 days after received.

WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application.
Contents under pressure.
Do not puncture or incinerate.
Do not expose to heat or temperatures above 49°C (120°F).
Usual Dosage:
See prescribing information.

NDC 72356-101-03

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

AMZEEQ Physician Sample Labels for Country-of-Origin Portugal

NDC 72356-101-90

Physician Sample
Not for Sale

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

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101L1004

NDC 72356-**101**-90
Physician Sample Not for Sale

amzeeq®
(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use
Rx only

VYNE™ THERAPEUTICS

7 g

Store at 2°C to 25°C (36°F to 77°F) until dispensed to the Physician or Patient.
Once dispensed, store AMZEEQ at room temperature 68-77°F (20-25°C).
Do not store in the refrigerator.
Shake can well before use.

WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure.
Do not puncture or incinerate.
Do not expose to heat or temperatures above 120°F (49°C).

Usual Doage: See prescribing information.

NDC 72356-101-90

Physician Sample Not for Sale

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

AMZEEQ Trade Labels for Country-of-Origin Switzerland

NDC 72356-101-03

Amzeeq®

(minocycline)
topical foam, 4%

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Rx only

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NDC 72356-**101**-03

amzeeq®
(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

VYNE™ THERAPEUTICS

30 g

Must be refrigerated, store at 2°C to 8°C (36°F to 46°F) until dispensed to the patient.
Once dispensed, the patient is to store AMZEEQ at room temperature below 25°C (77°F) for 90 days.
Do not store in the refrigerator.
Allow the can to warm to room temperature before first use.
Shake can well before use.

Date received from pharmacy / /
Discard unused portion 90 days after received.

WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application.
Contents under pressure.
Do not puncture or incinerate.
Do not expose to heat or temperatures above 49°C (120°F).
Usual Dosage:
See prescribing information.

NDC 72356-101-03

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

AMZEEQ Physician Sample Labels for Country-of-Origin Switzerland

NDC 72356-101-90

Physician Sample
Not for Sale

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

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101M1001

NDC 72356-101-90
Physician Sample Not for Sale

amzeeq®
(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use
Rx only

VYNE THERAPEUTICS

7 g

Store at 2°C to 25°C (36°F to 77°F) until dispensed to the Physician or Patient.
Once dispensed, store AMZEEQ at room temperature 68-77°F (20-25°C).
Do not store in the refrigerator.
Shake can well before use.

WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure.
Do not puncture or incinerate.
Do not expose to heat or temperatures above 120°F (49°C).

Usual Doage: See prescribing information.

NDC 72356-101-90

Physician Sample Not for Sale

Amzeeq®

(minocycline)
topical foam, 4%

For topical use only, not for oral, ophthalmic or intravaginal use

Rx only

AMZEEQ
minocycline aerosol, foam

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72356-101
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MINOCYCLINE HYDROCHLORIDE (UNII: 0020414E5U) (MINOCYCLINE - UNII:FYY3R43WGO)	MINOCYCLINE	40 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
HYDROGENATED SOYBEAN OIL (UNII: A2M91M918C)	
COCONUT OIL (UNII: Q9L0O73W7L)	
LIGHT MINERAL OIL (UNII: N6K5787QVP)	

CYCLOMETHICONE (UNII: NMQ347994Z)	
CETOSTEARYL ALCOHOL (UNII: 2DMT128M1S)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
MYRISTYL ALCOHOL (UNII: V42034O9PU)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
WHITE WAX (UNII: 7G1J5DA97F)	
STEARYL ALCOHOL (UNII: 2KR89I4H1Y)	
DOCOSANOL (UNII: 9G1OE216XY)	
BUTANE (UNII: 6LV4FOR43R)	
ISOBUTANE (UNII: BXR49TP611)	
PROPANE (UNII: T75W9911L6)	

Product Characteristics

Color	YELLOW	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72356-101-03	1 in 1 CARTON	01/02/2020	
1		30 g in 1 CAN; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:72356-101-90	1 in 1 CARTON	01/02/2020	
2		7 g in 1 CAN; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212379	01/02/2020	

Labeler - VYNE Pharmaceuticals Inc. (079786903)

Revised: 2/2021 VYNE Pharmaceuticals Inc.