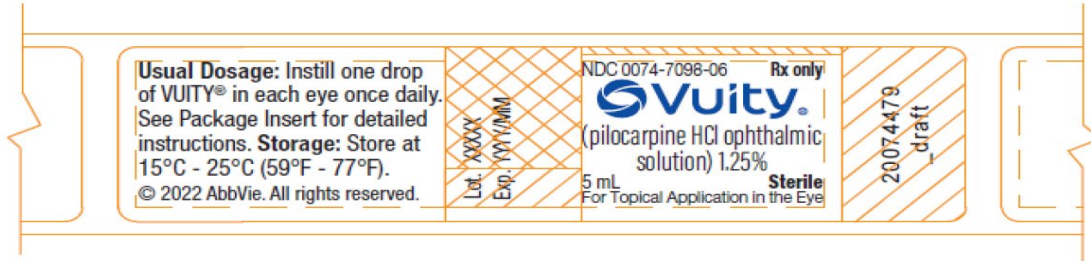


NDA 214028/S-003
Page 3

Container label



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VUITY safely and effectively. See full prescribing information for VUITY.

VUITY® (pilocarpine hydrochloride ophthalmic solution) 1.25%, for topical ophthalmic use

Initial U.S. Approval: 1974

RECENT MAJOR CHANGES

Warnings and Precautions, Blurred Vision (5.1) 8/2022
Warnings and Precautions, Risk of Retinal Detachment (5.2) 8/2022

INDICATIONS AND USAGE

VUITY is a cholinergic muscarinic receptor agonist indicated for the treatment of presbyopia in adults. (1)

DOSAGE AND ADMINISTRATION

Instill one drop of VUITY in each eye once daily. (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing pilocarpine hydrochloride 1.25%. (3)

CONTRAINDICATIONS

Hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- **Blurred Vision:** Patients should be advised not to drive or operate machinery if vision is not clear (e.g., blurred vision). Exercise caution in night driving and other hazardous activities in poor illumination. (5.1)
- **Risk of Retinal Detachment:** Rare cases of retinal detachment and retinal tear have been reported with miotics, including VUITY. Individuals with pre-existing retinal disease are at increased risk. Therefore, examination of the retina is advised in all patients prior to initiation of therapy. Patients should be advised to seek immediate medical care with sudden onset of flashing lights, floaters, or vision loss. (5.2)
- **Iritis:** Caution is advised in patients with iritis. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (>5%) are headache and conjunctival hyperemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: MM/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Blurred Vision
 - 5.2 Risk of Retinal Detachment
 - 5.3 Iritis
 - 5.4 Use with Contact Lenses
 - 5.5 Potential for Eye Injury or Contamination
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use

- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VUITY is indicated for the treatment of presbyopia in adults.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of VUITY is one drop in each eye once daily.

If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

VUITY (pilocarpine hydrochloride ophthalmic solution) is a clear, colorless, sterile ophthalmic solution containing 1.25% (12.5 mg/mL) of pilocarpine hydrochloride.

4 CONTRAINDICATIONS

VUITY is contraindicated in patients with known hypersensitivity to the active ingredient or to any of the excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Blurred Vision

Miotics, including VUITY, may cause accommodative spasm. Patients should be advised not to drive or operate machinery if vision is not clear (e.g., blurred vision).

In addition, patients may experience temporary dim or dark vision with miotics, including VUITY. Patients should be advised to exercise caution in night driving and other hazardous activities in poor illumination.

5.2 Risk of Retinal Detachment

Rare cases of retinal detachment and retinal tear have been reported with miotics, including VUITY.

Individuals with pre-existing retinal disease are at increased risk. Therefore, examination of the retina is advised in all patients prior to the initiation of therapy.

Patients should be advised to seek immediate medical care with sudden onset of flashing lights, floaters, or vision loss.

5.3 Iritis

VUITY is not recommended to be used when iritis is present because adhesions (synechiae) may form between the iris and the lens.

5.4 Use with Contact Lenses

Contact lens wearers should be advised to remove their lenses prior to the instillation of VUITY and to wait 10 minutes after dosing before reinserting their contact lenses.

5.5 Potential for Eye Injury or Contamination

To prevent eye injury or contamination, care should be taken to avoid touching the dispensing bottle to the eye or to any other surface.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hypersensitivity [*see Contraindications (4)*]

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.

VUITY was evaluated in 375 patients with presbyopia in two randomized, double-masked, vehicle-controlled studies (GEMINI 1 and GEMINI 2) of 30 days duration. The most common adverse reactions reported in >5% of patients were headache and conjunctival hyperemia. Ocular adverse reactions reported in 1-5% of patients were blurred vision, eye pain, visual impairment, eye irritation, and increased lacrimation.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VUITY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to VUITY exposure.

Eye disorders: vitreous detachment, vitreomacular traction, retinal tear, retinal detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VUITY administration in pregnant women to inform a drug-associated risk. Oral administration of pilocarpine to pregnant rats throughout organogenesis and lactation did not produce adverse effects at clinically relevant doses.

Data

Human Data

No adequate and well-controlled trials of VUITY have been conducted in pregnant women. In a retrospective case series of 15 women with glaucoma, 4 patients used ophthalmic pilocarpine either pre-pregnancy, during pregnancy or postpartum. There were no adverse effects observed in patients or in their infants.

Animal Data

In embryofetal development studies, oral administration of pilocarpine to pregnant rats throughout organogenesis produced maternal toxicity, skeletal anomalies and reduction in fetal body weight at 90 mg/kg/day (approximately 970-fold higher than the maximum recommended human ophthalmic dose [MRHOD] of 0.015 mg/kg/day, on a mg/m² basis).

In a peri-/postnatal study in rats, oral administration of pilocarpine during late gestation through lactation increased stillbirths at a dose of 36 mg/kg/day (approximately 390-fold higher than the MRHOD). Decreased neonatal survival and reduced mean body weight of pups were observed at ≥ 18 mg/kg/day (approximately 200 times the recommended human daily dose of VUITY).

8.2 Lactation

Risk Summary

There is no information regarding the presence of pilocarpine in human milk, the effects on the breastfed infants, or the effects on milk production to inform risk of VUITY to an infant during lactation.

Pilocarpine and/or its metabolites are excreted in the milk of lactating rats. Systemic levels of pilocarpine following topical ocular administration are low [see *Clinical Pharmacology (12.3)*], and it is not known whether measurable levels of pilocarpine would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Vuity and any potential adverse effects on the breastfed child from Vuity.

Data

Animal Data

Following a single oral administration of ¹⁴C-pilocarpine to lactating rats, the radioactivity concentrations in milk were similar to those in plasma.

8.4 Pediatric Use

Presbyopia does not occur in the pediatric population.

8.5 Geriatric Use

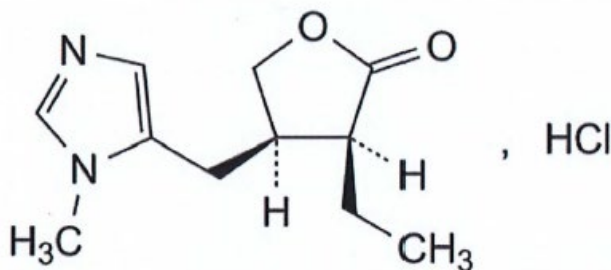
Clinical studies of Vuity did not include subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience with ophthalmic pilocarpine solutions have not identified overall differences in safety between elderly and younger patients.

10 OVERDOSAGE

Systemic toxicity following topical ocular administration of pilocarpine is rare, but occasionally patients who are sensitive may develop sweating and gastrointestinal overactivity. Accidental ingestion can produce sweating, salivation, nausea, tremors and slowing of the pulse and a decrease in blood pressure. In moderate overdose, spontaneous recovery is to be expected and is aided by intravenous fluids to compensate for dehydration. For patients demonstrating severe poisoning, atropine, the pharmacologic antagonist to pilocarpine, should be used.

11 DESCRIPTION

Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% is a cholinergic muscarinic receptor agonist prepared as an isotonic, clear, colorless, sterile ophthalmic solution containing 1.25% of pilocarpine hydrochloride. The chemical name for pilocarpine hydrochloride is (3S,4R)-3-ethyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]oxolan-2-one hydrochloride. Its molecular weight is 244.72 and its molecular formula is C₁₁H₁₆N₂O₂ · HCl. Its structural formula is:



Each mL of Vuity contains pilocarpine hydrochloride 1.25% (12.5 mg) as the active ingredient, equivalent to 1.06% (10.6 mg) pilocarpine free-base. Preservative is: benzalkonium chloride 0.0075%. Inactive ingredients in the ophthalmic solution are: boric acid, sodium citrate dihydrate, sodium chloride, purified water, and may also include hydrochloric acid and/or sodium hydroxide for pH adjustment to between 3.5 and 5.5, if necessary.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pilocarpine hydrochloride is a cholinergic muscarinic agonist which activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. VUITY contracts the iris sphincter muscle, constricting the pupil to improve near and intermediate visual acuity while maintaining some pupillary response to light. VUITY also contracts the ciliary muscle and may shift the eye to a more myopic state.

12.3 Pharmacokinetics

Systemic exposure to pilocarpine was evaluated in 22 participants with presbyopia who were administered 1 drop of VUITY in each eye once daily for 30 days. The mean C_{\max} and $AUC_{0-t,ss}$ values on Day 30 were 1.95 ng/mL and 4.14 ng·hr/mL, respectively. The median T_{\max} value on Day 30 was 0.3 hours postdose with a range from 0.2 to 0.5 hours postdose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Pilocarpine did not induce tumors in mice at any dosage level studied (up to 30 mg/kg/day; approximately 160-times the MRHOD). In rats, an oral dose of 18 mg/kg/day (approximately 200 times the MRHOD), resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both male and female rats, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats.

Mutagenesis

Pilocarpine did not show any potential to cause genetic toxicity in a series of studies that included: 1) bacterial assays (Salmonella and E. coli) for reverse gene mutations; 2) an in vitro chromosome aberration assay in a Chinese hamster ovary cell line; 3) an in vivo chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Impairment of Fertility

Pilocarpine oral administration to male and female rats at a dosage of 18 mg/kg/day (200 times the recommended human daily dose) resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on males, females, or both. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day for 6 months resulted in evidence of impaired spermatogenesis (approximately 110 times the recommended human daily dose).

14 CLINICAL STUDIES

The efficacy of VUITY for the treatment of presbyopia was demonstrated in two 30-Day Phase 3, randomized, double-masked, vehicle-controlled studies, namely GEMINI 1 (NCT03804268) and GEMINI 2 (NCT03857542). A total of 750 participants aged 40 to 55 years old with presbyopia were randomized (375 to VUITY group) in two studies and participants were instructed to administer one drop of VUITY or vehicle once daily in each eye.

In both studies, the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular distance corrected near visual acuity (DCNVA), without losing more than 1 line (5 letters) of corrected distance visual acuity (CDVA) with the same refractive correction was statistically significantly greater in the VUITY group compared to the vehicle group at Day 30, Hour 3 (see Table 1).

Table 1: Primary Efficacy Results from GEMINI 1 and GEMINI 2 Studies (Intent-to-Treat Population)

	GEMINI 1			GEMINI 2		
	VUITY N=163	Vehicle N=160	p-value	VUITY N=212	Vehicle N=215	p-value
Proportion of participants gaining 3-lines or more in mesopic DCNVA, without losing more than 1 line (5 letters) of CDVA at Day 30, Hour 3	31%	8%	p<0.01	26%	11%	p<0.01

Figures 1 and 2 present the proportion of participants who gained 3-lines or more in mesopic DCNVA at Day 30.

Figure 1: Proportion of Participants Achieving 3-Lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 1 (Intent-to-Treat Population)

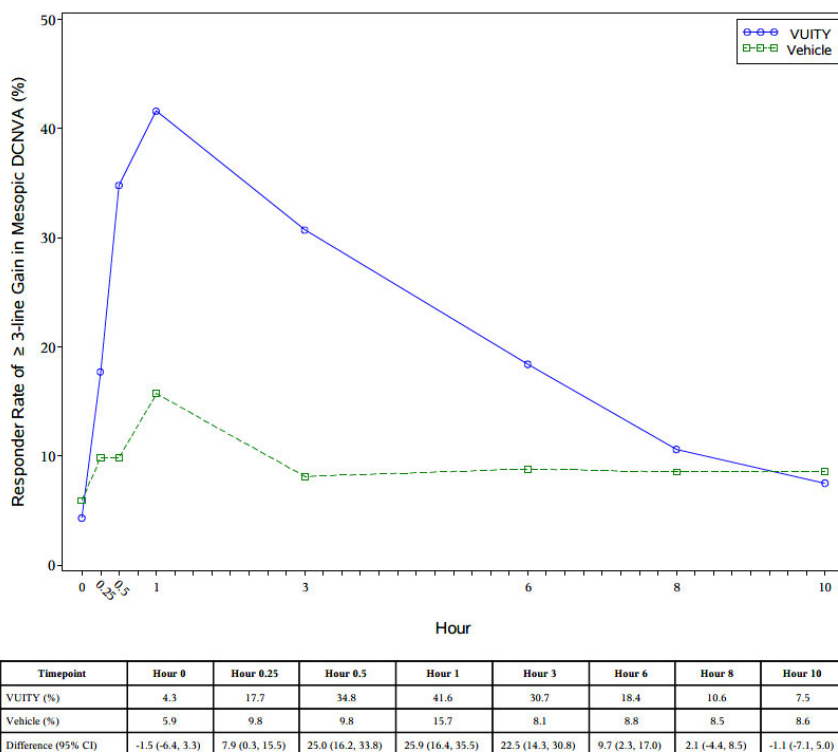
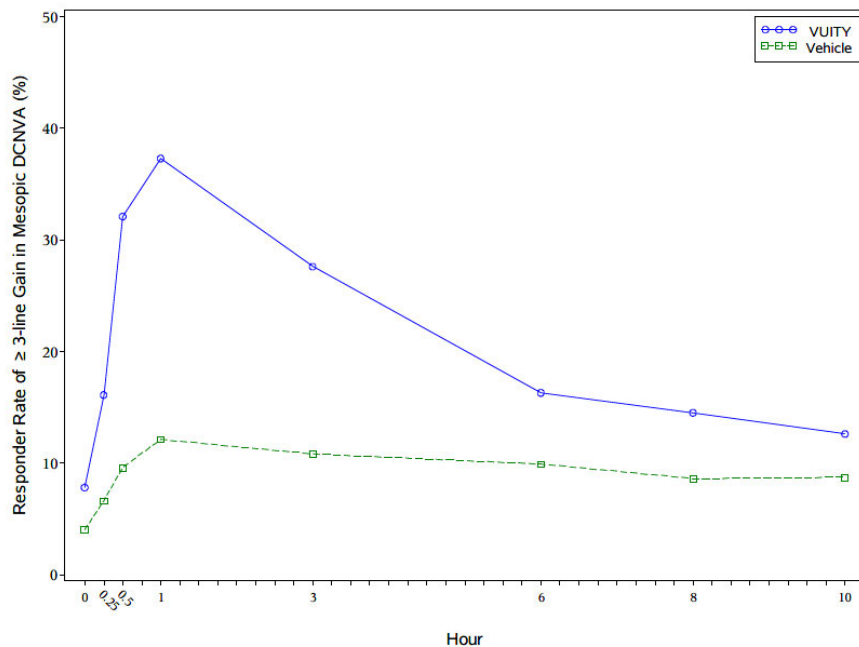


Figure 2: Proportion of Participants Achieving 3-lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 2 (Intent-to-Treat population)



Timepoint	Hour 0	Hour 0.25	Hour 0.5	Hour 1	Hour 3	Hour 6	Hour 8	Hour 10
Vuity (%)	7.8	16.1	32.1	37.3	27.6	16.3	14.5	12.6
Vehicle (%)	4.0	6.6	9.6	12.1	10.8	9.9	8.6	8.7
Difference (95% CI)	3.8 (-0.9, 8.4)	9.4 (3.2, 15.7)	22.5 (14.7, 30.3)	25.2 (17.0, 33.4)	16.7 (9.1, 24.3)	6.5 (-0.1, 13.1)	5.9 (-0.5, 12.2)	3.8 (-2.3, 10.0)

16 HOW SUPPLIED/STORAGE AND HANDLING

Vuity is supplied as a clear, colorless, sterile ophthalmic solution in colorless low density polyethylene (LDPE) ophthalmic dispenser bottles and tips, with dark green high impact polystyrene caps as follows:

2.5 mL fill in 5 mL bottle (Box containing 1 bottle)	NDC 0074-7098-01
2.5 mL fill in 5 mL bottle (Box containing 3 bottles)	NDC 0074-7098-03
2.5 mL fill in 5 mL bottle (Carton)	NDC 0074-7098-04
5 mL fill in 5 mL bottle (Carton)	NDC 0074-7098-06

Storage

Store at 15°C to 25°C (59°F to 77°F). After opening, Vuity can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Night Driving

VUITY may cause temporary dim or dark vision. Advise patients to exercise caution with night driving and when hazardous activities are undertaken in poor illumination. *[see Warnings and Precautions (5.1)]*

Accommodative Spasm

Temporary problems when changing focus between near and distant objects may occur. Advise patients not to drive or use machinery if vision is not clear (e.g., blurred vision). *[see Warnings and Precautions (5.1)]*

When to Seek Physician Advice

Advise patients to seek immediate medical care with sudden onset of flashing lights, floaters, or vision loss. *[see Warnings and Precautions (5.2)]*

Contact Lens Wear

Contact lens should be removed prior to the instillation of VUITY. Wait 10 minutes after dosing before reinserting contact lenses. *[see Warnings and Precautions (5.4)]*

Avoiding Contamination of the Product

Do not touch dropper tip to any surface, as this may contaminate the contents. *[see Warnings and Precautions (5.5)]*

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.



Vuity® and its design are registered trademarks of Allergan Sales, LLC

Distributed by: Allergan, an AbbVie Company

Manufactured for:

AbbVie Inc.

North Chicago, IL 60064 USA

Allergan is an affiliate of AbbVie Inc.

© 2022 AbbVie. All rights reserved.

North Chicago, IL, 60064, USA

Patented.

v3.0USPI7098



David
Lewis

Digitally signed by David Lewis

Date: 3/08/2023 01:12:26PM

GUID: 508da72000029f287fa31e664741b577

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARIA A CLARY
04/06/2023 11:45:31 AM