MEDISCA® NETWORK INC.
TECHNICAL SUPPORT SERVICES
FORMULATION CHEMISTRY DEPARTMENT
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Suggested Formula	Dorzolamide 2%, Timolol 0.5% Ophthalmic Drops (Solution, 20 mL)	FIN	F 008 793

SUGGESTED FORMULATION

Ingredient Listing	Qty.	Unit	NDC #	Supplier	Lot Number	Expiry Date
Dorzolamide Hydrochloride, USP*	0.444	g				
Timolol Maleate, USP)**	0.137	g				
Benzalkonium Chloride 1% Stock Solution †	0.15	mL				
Hydroxyethyl Cellulose (2200-6600 CPS), NF	0.08	g				
Sodium Citrate (Dihydrate), USP	0.20	g				
Mannitol, USP	0.03	g				
Sodium Chloride, USP	0.023	g				
Sterile Water for Injection, USP	17.0	mL				
Sterile Water for Injection, USP	q.s. to 20.0	mL				
Hydrochloric Acid 10% Solution	As required					
Sodium Hydroxide 10% Solution	As required					
† **Benzalkonium Chloride 1% Stock Solution**						
Benzalkonium Chloride Solution (50%), NF	0.2	mL				
Sterile Water for Injection, USP	9.0	mL				
Sterile Water for Injection, USP	q.s. to 10.0	mL				

* Dorzolamide Hydrochloride 0.444 g is equivalent to Dorzolamide 0.400 g.
** Timolol Maleate 0.137 g is equivalent to 0.100 g

SPECIAL PREPARATORY CONSIDERATIONS

Ingredient-Specific Information

Light Sensitive *(protect from light whenever possible):*	*Dorzolamide Hydrochloride, Benzalkonium Chloride Solution, Timolol Maleate*
Hygroscopic *(protect from moisture whenever possible):*	*Benzalkonium Chloride Solution, Hydroxyethyl Cellulose*
Air Sensitive *(protect from air whenever possible):*	*Benzalkonium Chloride Solution*
Metal Reactive *(protect from metals whenever possible):*	*Benzalkonium Chloride Solution*

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SPECIAL PREPARATORY CONSIDERATIONS (CONTINUED)

Suggested Preparatory Guidelines

☐ Non-Sterile Preparation ■ Sterile Preparation

Processing Error / Testing Considerations: To account for processing error, pH testing and sterility testing considerations during preparation, it is suggested to measure an additional **15 to 20%** of the required quantities of ingredients.

Special Instruction: This formula may contain one or more Active Pharmaceutical Ingredients (APIs) that may be classified as hazardous, please refer & verify the current NIOSH list of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. At this time, **General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings** is informational and not compendially applicable unless otherwise specified by regulators and enforcement bodies. For information on the scope, intended applicability, and implementation context for USP General Chapter <800>, see: https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare.

This formula must be prepared within the appropriate facilities under adequate environmental conditions, following the necessary guidelines and procedures as stated within *USP 797* and *USP 800*, when handling hazardous drugs. Only trained and qualified personnel must prepare this formula.

All heat stable, reusable materials and equipment must be sterilized and depyrogenated by dry heat sterilization at 250°C for 2 hours prior to use.

Compounder needs to verify as per USP, if every batch of final product compounded using this procedure must be sterility and endotoxin tested before being dispensed.

All required personal protective equipment (sterile and hazardous if applicable), such as but not limited to, gowns, aprons, sleeves, gloves both inner and outer if applicable, shoe covers, hairnet, head cap, beard cover, eyewear, appropriate face mask, respirator and face shield, etc., where applicable must be worn at all times. In addition, proper personnel cleansing must be done before entering the buffer or clean area.

If applicable, follow all required procedures for hazardous drug handling including but not limited to procurement, transport, storage, preparation, dispensing, administration, clean up (spills) & disposal.

Filter integrity must be validated by performing a filter stress test. If the test demonstrates that the filter might be defective, the solution must be discarded and remade.

If you are a registered 503B facility, please refer to all relevant guidance documents including but not limited to the Code of Federal Regulations (CFR), Guidance for Industry (GFIs) and Compliance Policy Guides (CPGs).

This procedure requires the use of very small quantities of ingredients. All calculations and preparation techniques must be verified before dispensing the final product.

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SUGGESTED PREPARATION (for 20 mL)

Weigh and / or measure the following ingredients when appropriate:

Ingredient Listing	Qty.	Unit	Multiplication factor (*): ____	Processing Error	Qty. to measure
Dorzolamide Hydrochloride, USP §	0.444	g			
Timolol Maleate, USP) §	0.137	g			
Benzalkonium Chloride 1% Stock Solution † §	0.15	mL			
Hydroxyethyl Cellulose (2200-6600 CPS), NF §	0.08	g			
Sodium Citrate (Dihydrate), USP §	0.20	g			
Mannitol, USP §	0.03	g			
Sodium Chloride, USP §	0.023	g			
Sterile Water for Injection, USP §	17.0	mL			
Sterile Water for Injection, USP §	q.s. to 20.0	mL			
Hydrochloric Acid 10% Solution §	As required				
Sodium Hydroxide 10% Solution §	As required				
† **Benzalkonium Chloride 1% Stock Solution**					
Benzalkonium Chloride Solution (50%), NF §	0.2	mL	---	---	
Sterile Water for Injection, USP §	9.0	mL	---	---	
Sterile Water for Injection, USP §	q.s. to 10.0	mL	---	---	

* Takes into account increased batch size conversions and density conversions, if required.
§ Weigh / measure just prior to use.

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Preparatory Instruction

IMPORTANT: All preparatory procedures must be performed using proper Aseptic Technique

1. **Equipment sterilization:**

   Following the manufacturer's specifications, sterilize and depyrogenate all heat stable, reusable materials and equipment, then return to ambient temperature.

2. † **Benzalkonium Chloride 1% Stock Solution preparation:**

   A. Incrementally add the Benzalkonium Chloride Solution (50%) (0.2 mL) to the Sterile Water for Injection (9.0 mL).

      Specifications: Continuously mix.

      End result: Homogeneous liquid-like solution.

   B. Add additional Sterile Water for Injection to the mixture (Step 3A) to fill to the required batch size (10.0 mL).

      Specifications: Continuously mix.

      End result: Homogeneous liquid-like solution.

3. **Powder-liquid preparation:**

   A. In the given order, sequentially add the following ingredients to the Sterile Water for Injection (17.0 mL *plus* processing error adjustments):

      -Benzalkonium Chloride 1% Stock Solution (0.15 mL *plus* processing error adjustments)
      -Hydroxyethyl Cellulose (2200-6600 CPS)
      -Dorzolamide Hydrochloride
      -Timolol Maleate
      -Sodium Citrate (Dihydrate)
      -Mannitol
      -Sodium Chloride

      Specifications: Continuously mix until all solid particles have completely dissolved.

      End result: Homogeneous liquid-like solution.

      Note: Add the next ingredient, once the previous one has been completely added and dissolved.

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4. **pH testing:**

A. Draw an appropriate amount of the mixture (Step 4A).

B. Test the pH of the sample. It should lie between 5.4 and 5.9.

C. If the pH < 5.4 carefully add, in a dropwise fashion, the Sodium Hydroxide 10% Solution to the mixture:

1. Draw and transfer 1 or 2 drops of the Sodium Hydroxide 10% Solution to the mixture.
2. Stir for at least 5 minutes to evenly disperse the Sodium Hydroxide 10% Solution.
3. Re-test the pH.
4. Continue to add the Sodium Hydroxide 10% Solution until the pH of 5.4 to 5.9 is obtained.

IMPORTANT: Do not allow the pH to rise above 5.9.

D. If the pH > 5.9, carefully add, in a dropwise fashion, the Hydrochloric Acid 10% Solution to the mixture:

1. Draw and transfer 1 or 2 drops of the Hydrochloric Acid 10% Solution to the mixture.
2. Stir for at least 5 minutes to evenly disperse the Hydrochloric Acid 10% Solution.
3. Re-test the pH.
4. Continue to add the Hydrochloric Acid 10% Solution until the pH of 5.4 to 5.9 is obtained.

IMPORTANT: Do not allow the pH to fall below 5.4.

5. **Filling to volume:**

A. Add additional Sterile Water for Injection to the above mixture to fill to the required batch size (20.0 mL *plus* processing error adjustments).

Specifications: Continuously mix.

End result: Homogeneous liquid-like solution.

6. **Filtering and transferring:**

Aseptically filter the solution through a 0.22-µm sterile filter into the recommended dispensing container (see Packaging requirements). Transfer the remainder into a separate dispensing container. This is to be used as the Test sample for sterility testing.

7. **Filter integrity test:**

Validate filter integrity by performing a filter stress test. If the test demonstrates that the filter might be defective, the solution must be discarded and remade.

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8.	**Terminal Sterilization:** In relation to the chemical composition of the formulation, final packaging, etc., select and validate an end-stage sterilization method and follow the manufacturer's specifications.
9.	**Sterility testing:** Validate the Test samples for sterility, in accordance to current USP 797 regulatory guidelines.

SUGGESTED PRESENTATION

Estimated Beyond-Use Date		24 hours controlled room temperature or 3 days refrigerated, as per USP 797.	Packaging Requirements		Sterile, tightly closed, light-resistant ophthalmic dropper bottles.
Auxiliary Labels	1	Use as directed. Do not exceed prescribed dose.	7		May impair mental and/or physical ability. Use care when operating a car or machinery.
	2	Keep out of reach of children.	8		Discard in the presence of particulate matter.
	3	Keep at controlled room temperature, (20°C – 25°C) or refrigerated (2°C – 8°C). **Do not freeze.**	9		Consult your health care practitioner if any prescription or over-the-counter medications are currently being used or are prescribed for future use.
	4	Do not use if discolored.	10		For ophthalmic use only.
	5	Cap tightly after use.	11		Equilibrate to room temperature before use.
	6	Protect from light.			
Pharmacist Instructions		Add any auxiliary labels specific to the API to the dispensing container as deemed necessary.			
Patient Instructions		Contact your pharmacist in the event of adverse reactions. **IMPORTANT:** The quantity of API administered is directly dependent on the quantity of product applied.			

REFERENCES

1.	Ophthalmic, Otic, and Nasal Preparations. In: Allen, LV, Jr. *The Art, Science, and Technology of Pharmaceutical Compounding Fifth Edition.* American Pharmacists Association; 2016: 317.
2.	Apo-Timol. In: Canadian Pharmacists Association. *Compendium of Pharmacists and Specialties, 2017*: 295.
3.	Hydroxytethyl Cellulose. In: Sheskey, P.J., ed. *Handbook of Pharmaceutical Excipients, 8th Edition*. Pharmaceutical Press and American Pharmacists Association; 2017: 446.

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4.	Mannitol. In: Sheskey, P.J., ed. *Handbook of Pharmaceutical Excipients, 8th Edition*. Pharmaceutical Press and American Pharmacists Association; 2017: 583.
5.	Benzalkonium Chloride. In: Sheskey, P.J., ed. *Handbook of Pharmaceutical Excipients, 8th Edition*. Pharmaceutical Press and American Pharmacists Association; 2017: 96.
6.	Sodium Chloride. In: Sheskey, P.J., ed. *Handbook of Pharmaceutical Excipients, 8th Edition*. Pharmaceutical Press and American Pharmacists Association; 2017: 854.
7.	Sodium Citrate Dihydrate. In: Sheskey, P.J., ed. *Handbook of Pharmaceutical Excipients, 8th Edition*. Pharmaceutical Press and American Pharmacists Association; 2017: 858.
8.	Dorzolamide Hydrochloride. In: Brayfield, A., ed. *Martindale: The Complete Drug Reference, 38th Edition.* London, England: The Pharmaceutical Press; 2014: 2006.
9.	Timolol Maleate. In: Brayfield, A., ed. *Martindale: The Complete Drug Reference, 38th Edition.* London, England: The Pharmaceutical Press; 2014: 15138.
10.	Dorzolamide (Monograph). In: O'Neil MJ. *The Merck Index 15th Edition*. Whitehouse Station, NJ: Merck & Co, Inc.; 2013: Monograph #3475.
11.	Timolol (Monograph). In: O'Neil MJ. *The Merck Index 15th Edition*. Whitehouse Station, NJ: Merck & Co, Inc.; 2013: Monograph #96012.
12.	Chapter 8: Buffered and Isotonic Solutions. In: Sinko, D. J. and Singh, Y. *Martin's Physical Pharmacy and Pharmaceutical Sciences, Sixth Edition.* Philadelphia, PA: Lipponcott Williams & Wilkins; 2011: 163-181.
13.	Chapter 18: Tonicity, Osmoticity, Osmolality and Osmolarity. In: D.B Troy. *Remington: The Science and Practice of Pharmacy, 21st Edition.* Baltimore, MD: Lippincott Williams & Wilkins; 2006: 250~265.
14.	Timolol Maleate. In: Trissel LA. *Trissel's Stability of Compounded Formulations, 5th Edition.* American Pharmaceutical Association; 2012: 477.
15.	Dorzolamide Hydrochloride (Monograph). *United States Pharmacopeia XLIII / National Formulary 38.* Rockville, MD. US Pharmacopeial Convention, Inc. 2020: 1496.
16.	Timolol Maleate (Monograph). *United States Pharmacopeia XLIII / National Formulary 38.* Rockville, MD. US Pharmacopeial Convention, Inc. 2020: 4387.
17.	USP <797>. *United States Pharmacopeia XLIII / National Formulary 38.* Rockville, MD. US Pharmacopeial Convention, Inc. 2020: 7037.