

Certificate of Analysis

Tilidine HCl

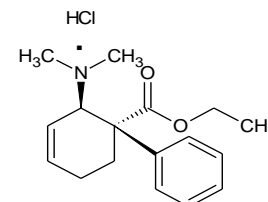
Cerilliant Quality

ISO GUIDE 34
CERTIFICATE ARI 353

ISO/IEC 17025
CERTIFICATE ATI 352

ISO 9001:2008
CERTIFICATE 3854

Catalog Number: T-068
Solution Lot: FE021811-01
Expiration: April 2016
Solvent: Methanol
Volume per Ampule: Not less than 1 mL
Storage: Store in freezer.
Intended Use: For R&D/ analytical purposes only. Not suitable for human or animal consumption.
Regulatory: USDEA Exempt | Canadian TK # 61-620



Safety: Danger. See Safety Data Sheet

- Expiration Date has been established through real time stability studies.
- Ampules are overfilled to ensure a minimum 1 mL volume fill. We advise laboratories to use measured volumes of this standard solution before diluting to the desired concentration.
- For quantitative applications, the minimum sample size for intended use is 1 μ L.

| Component | Chromatographic Purity | Certified Concentration |
|--|------------------------|--|
| Tilidine HCl | 98.9% | 1.000 \pm 0.006 mg/mL (as free base) |
| <ul style="list-style-type: none"> Uncertainty of the concentration is expressed as an expanded uncertainty in accordance with ISO 17025 and Guide 34 at the approximate 95% confidence interval using a coverage factor of $k = 2$ and has been calculated by statistical analysis of our production system and incorporates uncertainty of the purity factor, material density, and balance and weighing technique. Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics. | | |

Solution Standard Verification and Homogeneity

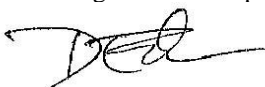
| Standard Solution | Lot Number | Verified Concentration (mg/mL) | | %RSD - Homogeneity | |
|---|-------------|--------------------------------|---------------------|--------------------|---------------------|
| | | Actual Results | Acceptance Criteria | Actual Results | Acceptance Criteria |
| New Lot | FE021811-01 | 0.999 | $\pm 3\%$ | 0.3 | $\leq 3\%$ |
| <ul style="list-style-type: none"> Concentration is verified through multiple analyses and is calculated as the average of multiple analyses compared to an independently prepared calibration solution. Homogeneity of the New Lot is ensured through rigorous production process controls statistically analyzed to evaluate risk and verified by analysis. The % RSD of samples pulled from across the lot demonstrate homogeneity of the New Lot. | | | | | |

Traceability

- Gravimetrically prepared using qualified balances calibrated semi-annually by Mettler Toledo using NIST traceable weights. Calibration verification performed weekly and prior to each use utilizing NIST traceable weights. Each balance has been assigned a minimum weighing by Mettler Toledo taking into consideration the balance and installed environmental conditions to ensure weighing complies with USP tolerances of no more than 0.1% relative error.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared using balances calibrated to NIST.
- In addition, each neat material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques. Spectral data is provided on subsequent pages of the COA.

Cerilliant certifies that this standard meets the specifications stated in this certificate and warrants this product to meet the stated acceptance criteria through the expiration/retest date when stored unopened as recommended. Product should be used shortly after opening to avoid concentration changes due to evaporation. Warranty does not apply to ampoules stored after opening.




Darron Ellsworth, Quality Assurance Manager

December 10, 2015

Date

| <i>Standard Solution Assay Parameters</i> | | <i>Calibration Curve</i> | |
|---|--------|---------------------------|-------------------|
| Analysis Method: | UV/Vis | Calibration Curve: | Linear Regression |
| Wavelength: | 227 nm | Number of Points: | 4 |
| Slit Width: | 1.0 nm | Linearity (r): | 1.000 |
| Response: | 0.5 s | | |

| <i>Neat Material Data</i> | | | |
|---------------------------|--------------|--------------------------|--|
| Compound Name: | Tilidine HCl | Chemical Formula: | C ₁₇ H ₂₃ NO ₂ •HCl |
| Compound Lot: | PC012511-01 | CAS Number: | 27107-79-5 |
| | | Molecular Weight: | 309.83 |

Neat Material Characterization Summary

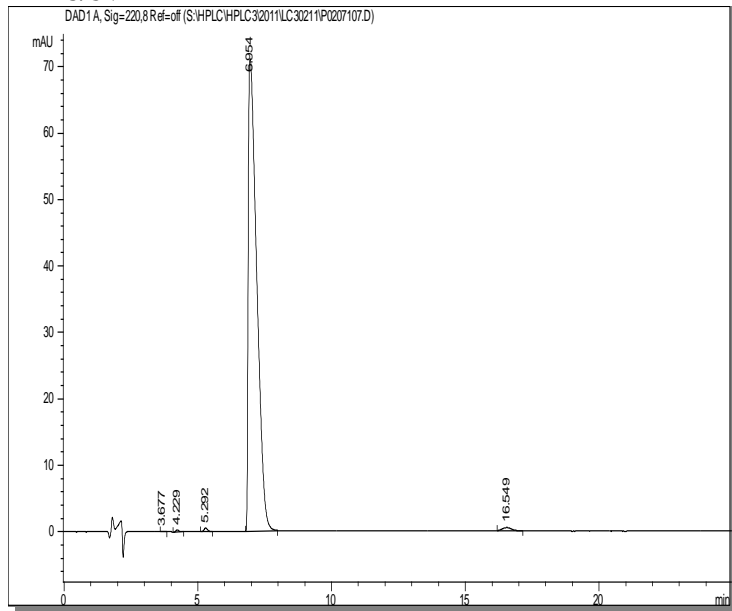
| Analytical Test | Method | Results |
|--|----------------------|------------------------------------|
| Primary Chromatographic Purity by HPLC/UV Analysis | SP10-0102 | 98.9% |
| Secondary Purity Analysis by Thin Layer Chromatography | SP10-0106 | Single Spot, R _f = 0.68 |
| Identity by LC/MS Analysis | SP10-0107 | Consistent with Structure |
| Identity by ¹ H-NMR Analysis | USP <761>, SP10-0116 | Consistent with Structure |
| Residual Solvent Analysis by GC/FID Headspace | AM1087 ¹ | None Detected |
| Residual Water Analysis by Karl Fischer Coulometry | USP <921>, SP10-0103 | 2.73% |
| Inorganic Content by Microash Analysis | SP10-0135 | < 0.2% |
| Purity Factor | | 96.21% |

- ♦ Primary purity is calculated as the average of two independently performed analyses utilizing two different methods. Acceptance criteria requires the purity values to be within 0.5% of each other.
- ♦ The primary chromatographic purity value is used to calculate the Purity Factor.
- ♦ A secondary purity method is utilized as a control.
- ♦ Purity Factor = [(100 - wt% residual solvent - wt% residual water - wt% residual inorganics) x Chromatographic Purity/100].
- ♦ Purity factor does not include adjustment for chiral and/or isotopic purity.

¹ Validated analytical method

Spectral and Physical Data

HPLC/UV

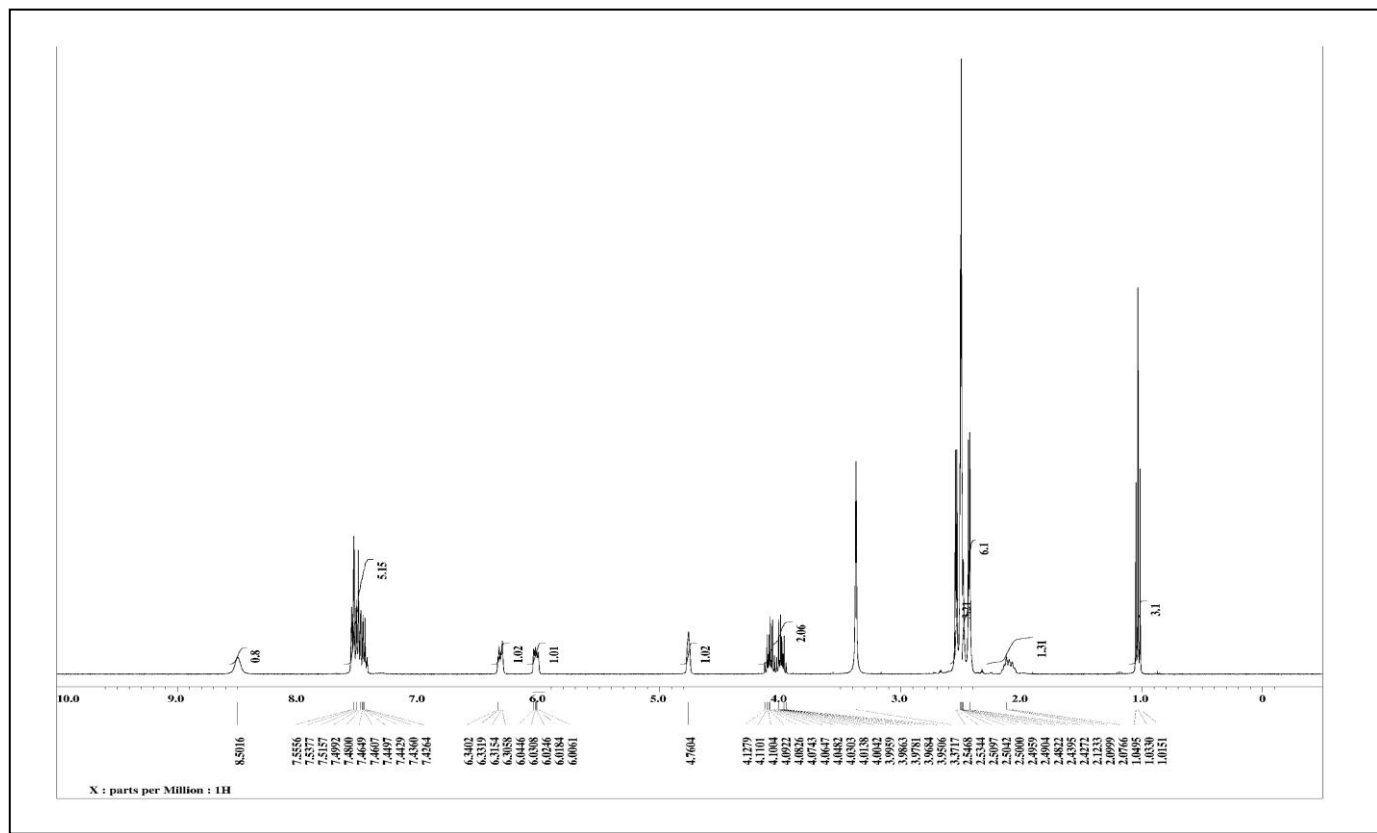


Column: Betasil Phenyl, 5 µm, 4.6 x 150 mm
Mobile Phase: Acetonitrile::10 mM Potassium phosphate buffer (30::70)
Flow Rate: 1.0 mL/min
Wavelength: 220 nm
Data File Name: S:\HPLC\HPLC3\2011\LC30211\P0207107.D
Instrument: LC#3
Sample Name: PC012511-01
Acquired: February 07, 2011

| Peak # | Ret Time | Area | Height | Area % |
|--------|----------|---------|--------|--------|
| 1 | 3.68 | 0.37 | 0.05 | 0.02 |
| 2 | 4.23 | 2.47 | 0.32 | 0.16 |
| 3 | 5.29 | 4.99 | 0.56 | 0.32 |
| 4 | 6.95 | 1564.54 | 71.16 | 98.77 |
| 5 | 16.55 | 11.61 | 0.49 | 0.73 |

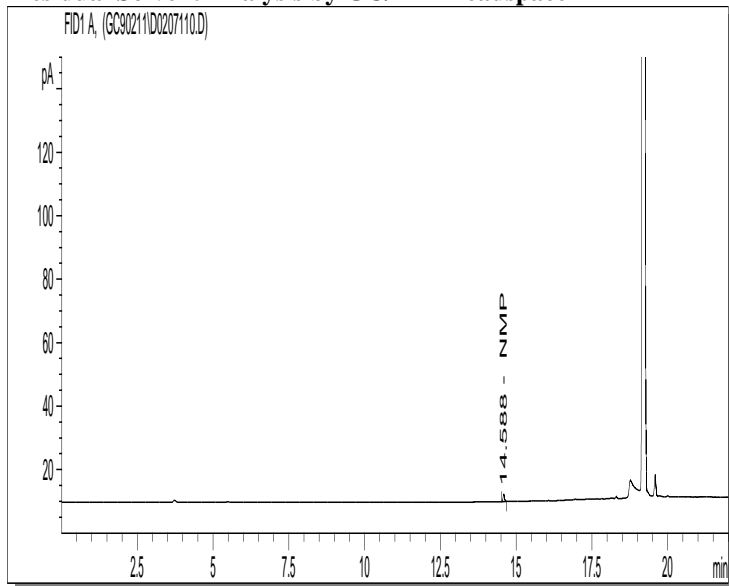
¹H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D₆



Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program: 40°C (12 min) to 220°C at 40°C/min (5.5 min)
Carrier Gas: Helium
Flow Rate: 2.0 mL/min
Detector Heater Temp: 250°C
Injector: Headspace Sampler
HS Oven Temp: 60°C
Vial Equilibration: 10 minutes

Data File Name: C:\CHEM32\1\DATA\GC90211\D0207110.D
Instrument: GC#9
Sample Name: PC012511-01
Acquired: February 07, 2011

| Peak | Compound | Area | Weight % |
|--------------|----------|------|-----------|
| 1 | NMP | NA | NA |
| Total | | | ND |

ND - None Detected

Spectral and Physical Data (cont.)

LC/MS

Column: Luna C₁₈, 3 μm, 2.0 x 100 mm

Mobile Phase: A:: Acetonitrile

B:: 0.1% Formic acid in Water

Gradient:

| Time (min) | %A | %B |
|------------|----|----|
| 0.0 | 10 | 90 |
| 5.0 | 50 | 50 |
| 15.0 | 50 | 50 |
| 20.0 | 50 | 50 |

Flow Rate: 0.3 mL/min

Scan Range: 100-1000 amu

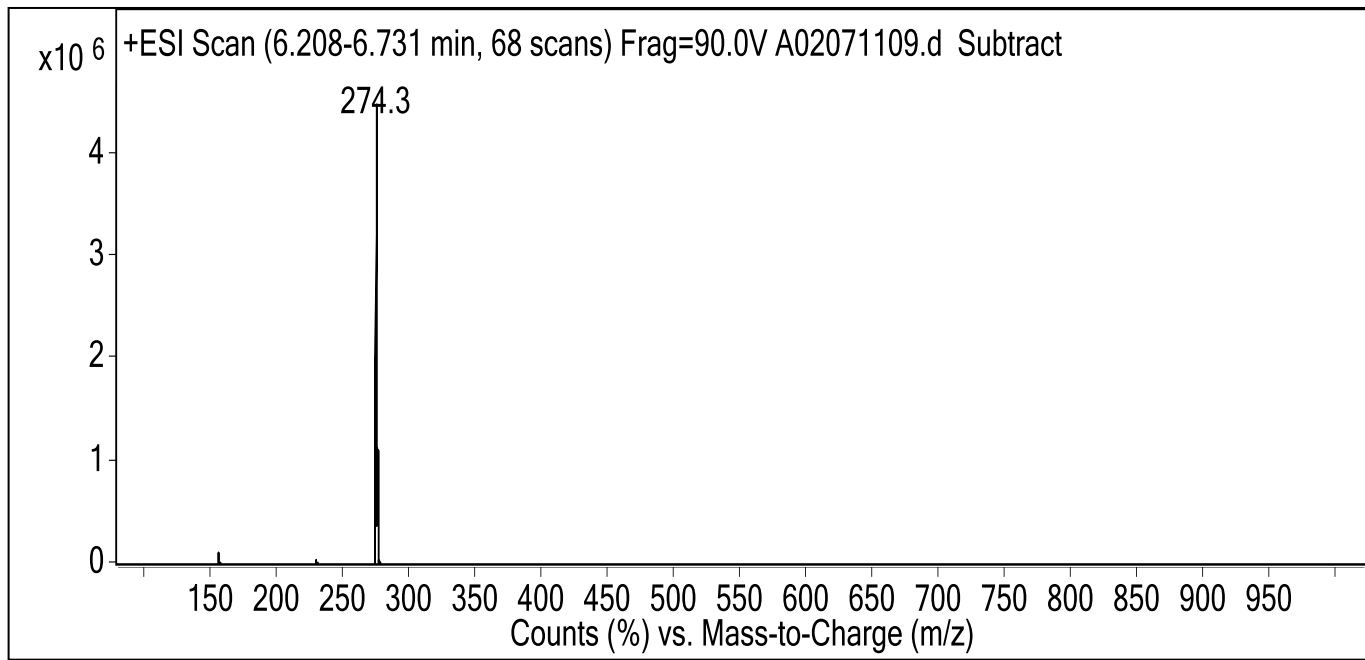
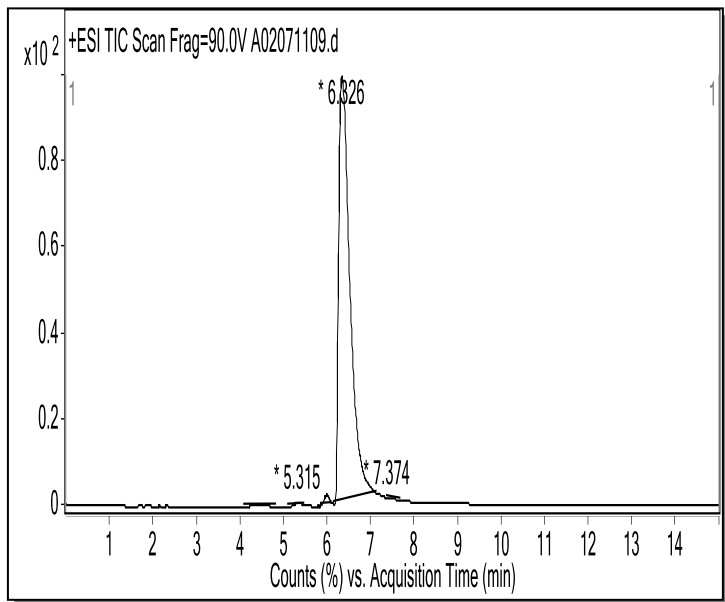
Ionization: Electrospray, Positive Ion

Data File Name: A02071109.d

Instrument: LC/MS/MS

Sample Name: PC012511-01

Acquired: February 07, 2011



Stability

Short Term Stability : A summary of accelerated stability findings for a related product (T-069, Tilidine-D₆ HCl) is listed below.

| Storage Condition | Mean Kinetic Temperature (MKT) | Time Period |
|-------------------|--------------------------------|---|
| Freezer | -15°C | No decrease in purity was noted after four weeks. |
| Refrigerator | 4°C | |
| Room Temperature | 21°C | |
| 40°C | 40°C | 0.7% decrease in purity was noted after four weeks. |

Transport/Shipping : Ship cold.

Short Term Storage: Stability data supports short term storage up to one year at Refrigerate conditions.

Long Term Stability: Long term stability has been assessed for freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 57 months has been established through real-time stability studies.

COA Revision History

| Revision No. | Date | Reason for Revision |
|--------------|--------------------|--|
| 00 | March 02, 2011 | Initial version |
| 01 | June 30, 2011 | Revised Storage condition from "Refrigerate or freeze" to "Store in freezer." |
| 02 | January 12, 2012 | Revised Retest Date from April 2012 to April 2013. |
| 03 | February 20, 2013 | Revised Retest Date from April 2013 to March 2014. |
| 04 | September 23, 2013 | Updated Stability Section with 4-week study data, including changing Shipping conditions to 'Ship Cold.' |
| 05 | March 07, 2014 | Revised Retest Date from March 2014 to January 2015. |
| 06 | December 30, 2014 | Revised Retest Date from January 2015 to December 2015. |
| | | Added minimal sample size statement to front page. |
| 07 | May 06, 2015 | Updated Safety Section from "Flammable, Poison" to "Danger. See Safety Data Sheet" |
| | | Added 20.0 min to LC/MS Gradient table. |
| 08 | October 06, 2015 | Revised Retest Date from December 2015 to April 2016. |
| | | Updated Long Term Stability from 46 months to 56 months. |
| 09 | December 10, 2015 | Revised Retest Date of April 2016 to Expiration Date April 2016. |
| | | Updated Long Term Stability from 56 months to 57 months. |