IV Compatibility Product

Trissel's Drugs and Solutions Data
Midazolam Hydrochloride

Trade Name(s)

VERSED

pH Range [90563] [71508]

pH 2.9 to 3.7

Formulation [90563]

Provided as colorless to light yellow liquid injections of midazolam 5 mg/mL and 1 mg/mL as the hydrochloride salt with sodium chloride 8 mg/mL, disodium edetate 0.1 mg/mL, and hydrochloric acid and/or sodium hydroxide to adjust pH during manufacturing in water for injection. Preserved forms containing benzyl alcohol 10 mg/mL and preservative-free forms are available.

Reconstitution [90563] [65407]

Midazolam hydrochloride injections may be administered intramuscularly or slowly intravenously without dilution. It may also be diluted in dextrose 5% or sodium chloride 0.9% for intravenous infusion.

Osmolality [90563] [71508]

Midazolam 5 mg/mL as hydrochloride injection is slightly hypertonic having an osmolality of 385 mOsm/kg.

Schneider et al. reported that Roche midazolam diluted in sodium chloride 0.9% to concentrations of 0.625 to 1.67 mg/mL had osmolalities of 274 to 259 mOsm/kg.

SodiumContent [65407]

Midazolam hydrochloride injections provide sodium 0.14 mEq/mL.

Storage [90563]

Store intact containers at controlled room temperature, and protect from exposure to light.

Maximum Stability [11447] [48663] [89062]

Maximum reported stability periods:
In D5W- 36 days refrigerated and at room temperature.

In NS- 3 months refrigerated and at room temperature. See Stability.

Stability (Detailed) [11447] [65407] [30205] [36673] [48663] [34005] [72924]

Intact vials of midazolam hydrochloride injection stored as directed by the manufacturer are stable until the labeled expiration date.

Infusion Solutions:
The manufacturer indicates that midazolam 0.5 mg/mL or lower as the hydrochloride salt is physically and chemically stable in dextrose 5% and sodium chloride 0.9% for 24 hours at room temperature and in lactated Ringer’s for 4 hours at room temperature.

Packaged in Syringes:
Several studies have evaluated the stability of midazolam hydrochloride undiluted and diluted in sodium chloride 0.9% packaged in various brands of polypropylene syringes. All of the studies have reported the drug to be stable for periods ranging from 10 days to 36 days at room temperature.

Peterson et al. reported that Roche midazolam 3 mg/mL as the hydrochloride diluted in sodium chloride 0.9% and packaged in Terumo polypropylene syringes was physically and chemically stable with HPLC analysis finding midazolam losses of 6.5% and 8.7% after 13 days at 20 °C and 32 °C, respectively.

Stiles et al. reported that Roche midazolam 2 mg/mL as the hydrochloride diluted in sodium chloride 0.9% and packaged in Pharmacia Deltec polypropylene infusion pump syringes was stable with stability-indicating HPLC analysis finding little change in the midazolam concentration in 10 days stored under refrigeration at 5 °C and at high room temperature of 30 °C.

Casasin Edo et al. reported that undiluted Roche midazolam injection 5 mg/mL as the hydrochloride packaged in Sherwood polypropylene syringes was stable for 36 days at room temperature of 25 °C protected from exposure to light with HPLC analysis found no loss of midazolam.

Pramar et al. reported that midazolam 1 mg/mL packaged in polypropylene syringes was stable for 4 weeks at room temperature shielded from exposure to direct sunlight with spectrophotometric and potentiometric analyses finding little change in the midazolam concentration.

Extemporaneous Injection:
Trissel and Hassenbusch evaluated the stability of compounded preservative-free midazolam 2.5- and 5-mg/mL (as hydrochloride) injection intended for investigational intrathecal administration. Midazolam (as hydrochloride) injection was prepared by dissolving midazolam powder in sodium chloride 0.9% to prepare the 2.5-mg/mL concentration and in sodium chloride 0.45% to prepare the 5-mg/mL concentration. The solutions had their pH values adjusted to pH 3.85 and 3.6, respectively, with 1 N hydrochloric acid. These pH values were designed to dissolve the powder and insure that the solution pH was sufficient to retain the midazolam in solution. The colorless to slightly yellow intrathecal 2.5- and 5-mg/mL injections had osmolalities of 316 and 200 mOsm/kg, respectively. The intrathecal injections were passed through 0.22-micron Millex filters into 20-mL Type I flint glass vials and sealed with rubber closures. The sealed vials were sterilized by autoclaving at 121 °C for 30 minutes with little or no loss of the midazolam content. Samples of each concentration were stored at 4, 23, and 37 °C. Stability-indicating HPLC analysis found 4% or less loss of midazolam after 3 months of storage at all of the storage temperatures.

Paramedic Conditions:
McMullan et al. evaluated the stability of midazolam hydrochloride 5-mg/mL injection packaged in glass cartridges within autoinjectors (Meridian Medical Technologies) during 60 days of storage in emergency vehicles during spring and summer in 14 metropolitan areas. HPLC analysis found that the drug in intact containers retained 100% of its initial concentration and showed no degradation.

pH Effects [15087] [65407] [47386] [90053] [63591]

Midazolam hydrochloride is reported to be stable in the pH range of 3 to 3.6.

Forman and Souney reported that the water solubility of midazolam hydrochloride is dependent on pH; at or below pH 4 the drug exhibits good water solubility. However, at higher pH values lower water solubility and higher lipid solubility occurs.

Andersin and Tammilehto reported that increased rates of photodegradation accompany increasing pH from 1.3 to 6.4. See Light Exposure.

Solubility:
The aqueous solubility of midazolam hydrochloride is pH dependent. As the pH decreases, and the solution becomes more acidic, the drug's solubility increases as shown below. A vehicle with a pH of around 4 is required to dissolve midazolam to concentrations of 2 mg/mL.

Midazolam Hydrochloride Solubility-pH Profile at 25°C

pH Solubility (mg/mL)

>6.2 <0.1

6.2 0.24

5.1 1.09

3.8 3.67

3.4 10.3

2.8 >22

Interaction with Plastics [42938] [48663] [82412] [63472] [32485] [72924] [67504]

Midazolam hydrochloride at pH values usually occurring in normal admixture solutions has not been found to undergo substantial sorption to polyvinyl chloride (PVC), polyolefin plastics such as polyethylene, polypropylene (in syringes) or other syringe components, or glass containers. Midazolam losses that occurred have usually been less than 6%, and most often no loss was found.

However, Bianchi et al. reported that in a solution of midazolam 0.03 mg/mL as the hydrochloride salt in either dextrose 5% or sodium chloride 0.9%, increasing the solution pH from about 4.5 up to 7 with phosphate buffer results in extensive sorptive losses of midazolam of 8% in 1 hour, 20% in 6 hours, and 46% in 24 hours.

Filtration [11447]

Midazolam (as hydrochloride) 2.5 and 5 mg/mL injections were passed through 0.22-micron Millex filters. No drug loss due to sorption to the filters occurred.

Freezing [68671] [65407]

de Diego et al. evaluated the stability of undiluted midazolam hydrochloride 5 mg/mL injection and also diluted to 0.5 mg/mL in dextrose 5% in water when frozen at −19 °C to −21 °C. Stability-indicating HPLC analysis found no midazolam hydrochloride loss after 14 days of frozen storage.

AHFS states that midazolam hydrochloride injection has been reported to be stable when stored frozen for 3 days with thawing at room temperature.

LightEffects [90563] [47386] [82412]

Intact containers of midazolam hydrochloride should be protected from exposure to light during long-term storage. Andersin and Tammilehto reported exposure of Roche midazolam vials to direct sunlight caused a yellow discoloration to form in 1 month and about 8% loss of midazolam in 4 months.

For shorter-term exposure to light that occurs during handling, preparation, and administration, no special light protection is required. McMullin et al. reported that Roche midazolam 1 mg/mL in sodium chloride 0.9% with 1% benzyl alcohol was stable for 10 days at a room temperature of 23 °C both exposed to fluorescent light and shielded from exposure to light. Stability-indicating HPLC analysis found no change in the midazolam concentrations and no increase in photodegradation products.

Other Information [65407] [51979]

Other Drugs:
Midazolam hydrochloride is stated to be compatible for 8 hours mixed in the same syringe with the drugs noted below.

Fentanyl citrate

Glycopyrrolate

Hydroxyzine hydrochloride

Ketamine hydrochloride

Nalbuphine hydrochloride

Promethazine hydrochloride

Sufentanil citrate

Midazolam hydrochloride is incompatible with tramadol hydrochloride.

Multiple Drugs:
Study 1:
Targett et al. reported the physical and chemical stability of 5-drug combinations at 2 concentrations that included the drugs noted below. The mixture was packaged in Terumo polypropylene syringes with tip caps and stored at room temperature and under refrigeration. The mixtures were physically stable over 2 weeks. HPLC analysis found midazolam was stable for 14 days under refrigeration but was stable at room temperature for only 12 days at the higher concentration and 5 days at the lower concentration exhibiting more than 10% loss after those times. The other drugs were all stable throughout the 14-day study period at both storage temperatures.

Concentration 1-

Morphine tartrate 400 mg

Dexamethasone

sodium phosphate 8 mg

Droperidol 2 mg

Scopolamine

hydrobromide 20 mg

Midazolam HCl 5 mg

Concentration 2-

Morphine tartrate 40 mg

Dexamethasone

sodium phosphate 8 mg

Droperidol 2 mg

Scopolamine

hydrobromide 20 mg

Midazolam HCl 5 mg

Sodium chloride 0.9% qs 10 mL

Study 2:
Negro et al. evaluated the compatibility of morphine hydrochloride (Grunenthal) and also tramadol hydrochloride (Andromaco) in 3-, 4-, and 5-drug combinations with five other drugs, including midazolam hydrochloride, diluted in sodium chloride 0.9% in elastomeric pump reservoirs for subcutaneous infusion for palliative care in cancer patients when stored at room temperature of 25 °C and protected from exposure to light.

Morphine hydrochloride 1.68 mg/mL or

Tramadol hydrochloride 11.18 mg/mL

was tested with dexamethasone sodium phosphate (Merck) 0.44 mg/mL, haloperidol lactate (Esteve) 0.21 mg/mL, hyoscine butylbromide (Boehringer-Ingelheim) 1.68 mg/mL, metoclopramide hydrochloride 1.11 mg/mL, and midazolam hydrochloride (Roche) 0.5 mg/mL.

Morphine hydrochloride 5 mg/mL or

Tramadol hydrochloride 33.3 mg/mL

was tested with dexamethasone sodium phosphate (Merck) 1.33 mg/mL, haloperidol lactate (Esteve) 0.62 mg/mL, hyoscine butylbromide (Boehringer-Ingelheim) 5 mg/mL, metoclopramide hydrochloride 3.33 mg/mL, midazolam hydrochloride (Roche) 1.5 mg/mL.

All 3-, 4-, and 5-drug combinations that contained dexamethasone sodium phosphate with midazolam hydrochloride and/or haloperidol lactate resulted in precipitation immediately upon preparation. The precipitation was most likely free dexamethasone that formed due to the lower pH of the admixtures containing haloperidol lactate and/or midazolam hydrochloride.

All 3-, 4-, and 5-drug combinations without dexamethasone sodium phosphate or midazolam hydrochloride and/or haloperidol lactate remained physically compatible for 7 days.

pHmax

3.7

pHmean

3.3

pHmin

Reference Section

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