# Metal Scavenging Screening Kit Product Manual

Part Number K-MS-3


## This Kit Contains:

| Description | Size 15 mL | Quantity (Cartridges) |
|---|---|---|
| Biotage® MP-TMT | 1 g | 5 |
| ISOLUTE® Si-TMT | 1 g | 5 |
| ISOLUTE® Si-Thiol | 1 g | 5 |
| ISOLUTE® Si-Trisamine | 1 g | 5 |
| ISOLUTE® SCX-2 | 1 g | 5 |

Biotage®

Quickly and easily screen API product mixtures to determine optimum conditions for metal removal processes.

This kit provides metal scavengers in an easy to use screening evaluation format with concise instructions to enable rapid determination of a metal scavenging candidate for a contaminated API mixture.

For more information on metal scavenging in batch stir processes please contact your local Biotage representative, asking for information relating to Metal Screening Kit p/n K-MS-2.

Biotage supported resin and silica based metal scavengers are effective reagents for the removal of trace PGMs from catalyzed reactions to final APIs. They are applied in a variety of different industries, from pharmaceutical to fine chemical, from agrochemical to waste treatment.

# Contents

# Introduction

Biotage Supported metal scavengers are highly selective enabling chemists to reach metal purity goals. Precious metals such as Pd, Pt, Ru and Rh in organometallic catalysts are becoming more widespread in industrial synthesis due to atom economy and green credentials. These PGM group catalyzed reactions are commonly used in the manufacture of active pharmaceutical ingredients (APIs) and fine chemicals. Achieving tolerated limits for metal content is becoming increasingly more challenging, with 5 ppm (ingested), and 1 ppm (parenteral) API posing particular difficulties in downstream purification of Pd based chemistries.

Traditional methods to remove metals include chromatography, activated carbon, extraction, distillation and recrystallization but, these can offer poor selectivity and lead to high API loss. Biotage has assembled a tool kit to facilitate the process of metal screening and method development.

## Benefits of Biotage Bound Metal Scavengers

- Higher metal affinity: low Kd(Pd) relative to API
  Kd(Pd): excellent metal scavenging
- Fast kinetics/filtration at room temp: enhanced by heating
- Diverse solid supports: silica and polystyrene backbones
- Work flow compatible: generic, use in diverse conditions
- Minimal loss of API: less/no non-specific binding
- Higher purity of final product: no leachables
- Short development time: faster method optimization

The metal scavengers are industry proven and supported by a **comprehensive regulatory qualification support package** including:

- Certificate of Analysis
  (including extractables, chemical loading, full lot and batch identity)
- MSDS/SDS
- BSE/TSE
- Instructions and suggestions

Biotage metal scavengers are made in an **ISO9001:2008** compliant manufacturing facility and have served the pharmaceutical, drug discovery and fine chemical industries for many years. Each material is batch and **lot controlled**, with benefits of full traceability.

Our specific case studies have generated a wealth of in-house data and we are able to offer extensive advice on metal scavenging in a number of different application areas.

### Shelf-Life and Stability

The resin based materials have been designed to be **mechanically robust** and may be stirred vigorously without breakdown. The silica metal scavengers are based on bioanalytical grade silicas and can also be added in batch processes and stirred but they have optimum flow characteristics as utility as fixed beds in columns. The scavengers are **indefinitely shelf stable** and may be stored in closed containers at RT, or longer term in a cool (4 °C) environment.

The SPE 1 g/15 mL cartridges in this kit will typically scavenge Pd from 1mol% catalyzed reactions run at 1mmol scale. Each situation is different though, and it is important to adjust the sample for influencing factors such as solvent, impurity profile, pH and also structure of the API itself. For more information on this, please contact your local Biotage representative.

## Recommended Procedure

Metal scavengers can be applied directly to reaction mother liquors or to later stage, post extraction and purification stages. Many end-users apply the scavengers to final stage API synthesis as they are most effective in those environments.

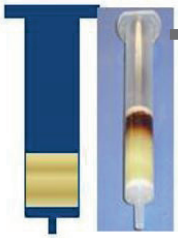
The kit contains metal scavengers in a 1 g/15 mL SPE cartridge. Due to the highly efficient nature of many Pd binding mechanisms with metal scavenger, once a hit is identified, this fixed-bed format may be directly scaled.

As a guide, based on normal assumptions made for many of the influencing factors involved in metal scavenging, a 1 g cartridge of metal scavenger is a good starting point to evaluate the product of a metal catalyzed reaction that used 1–2 mol % catalyst at 1 mmol scale.

1. **Equilibrate** cartridge by passing 3–5 bed volumes of API / product solvent through. This will remove any air gaps and enhance the scavenging process. This step is not critical if the cartridge is to be used under capacity.
2. **Add dissolved product** to cartridge and allow it to flow through under gravity at room temperature. Placing the cartridges on Biotage Gravity Rack is an easy way to support testing of up to 20 materials in a screen. The sample in the cartridge may be ‘pushed’ using slight air or nitrogen pressure from the top or it may be ‘pulled’ gently, using light vacuum (this method is especially amenable to processing on Biotage® FlashVac).
3. Palladium (even in ‘clear colorless’ solutions) on scavenging may cause Si-TMT to change color. It is normal to see a dark brown/black band of Pd at the top of the silica bed. It is one possible visual indication of metal scavenging, however depending on the system being scavenged, the color may not be very noticeable.

4. Once product has passed through, wash cartridge with 5 bed volumes of solvent (if the API is not retained, this step may be omitted to further improve atom economy). In our testing, Breakthrough of Pd was not observed, even following multiple (50+) bed volume washes using solvent under extreme testing, so the cartridge may be washed as necessary without fear of re-contaminating the filtrate with Pd, during removal of the API or organic compound.
5. Chemical products are generally not retained on neutral metal scavengers such as Si-Thiol or MP and Si-TMT, so washing can be kept to a minimum. For the two scavengers which can additionally utilize an ion exchange retention mechanism (ISOLUTE® SCX-2 and ISOLUTE® Si-Trisamine) it is important to factor in the acid/base characteristics of the API itself. Depending on structure, some compounds may require more washing for complete elution.

1. Add metal contaminated API solution



2. Asses final metal level

3. Evaluate ppm data

| | Biotage® MP-TMT | ISOLUTE® Si-TMT | ISOLUTE® Si-Thiol | ISOLUTE® SCX-2 | ISOLUTE® Si- Trisamine |
|---|---|---|---|---|---|
| ppm Pd start | 500 | 500 | 500 | 500 | 500 |
| ppm Pd end | ? | ? | ? | ? | ? |

Representative and optional experimental set-up for screening experiments (see Ordering Information on page 14 for more detailed information).

**Bulk Metal Scavengers: ISOLUTE® Si-TMT**
9538-0010 (10 g)
9538-0025 (25 g)
9538-0100 (100 g)
9538-1000 (1 Kg)

**Bulk Metal Scavengers: Biotage® MP-TMT**
801469 (10 g)
801470 (25 g)
801471 (100 g)
801472 (1 Kg)

**Bulk Metal Scavengers: ISOLUTE® SCX-2**
9536-0010 (10 g)
9536-0025 (25 g)
9536-0100 (100 g)
9536-1000 (1 Kg)

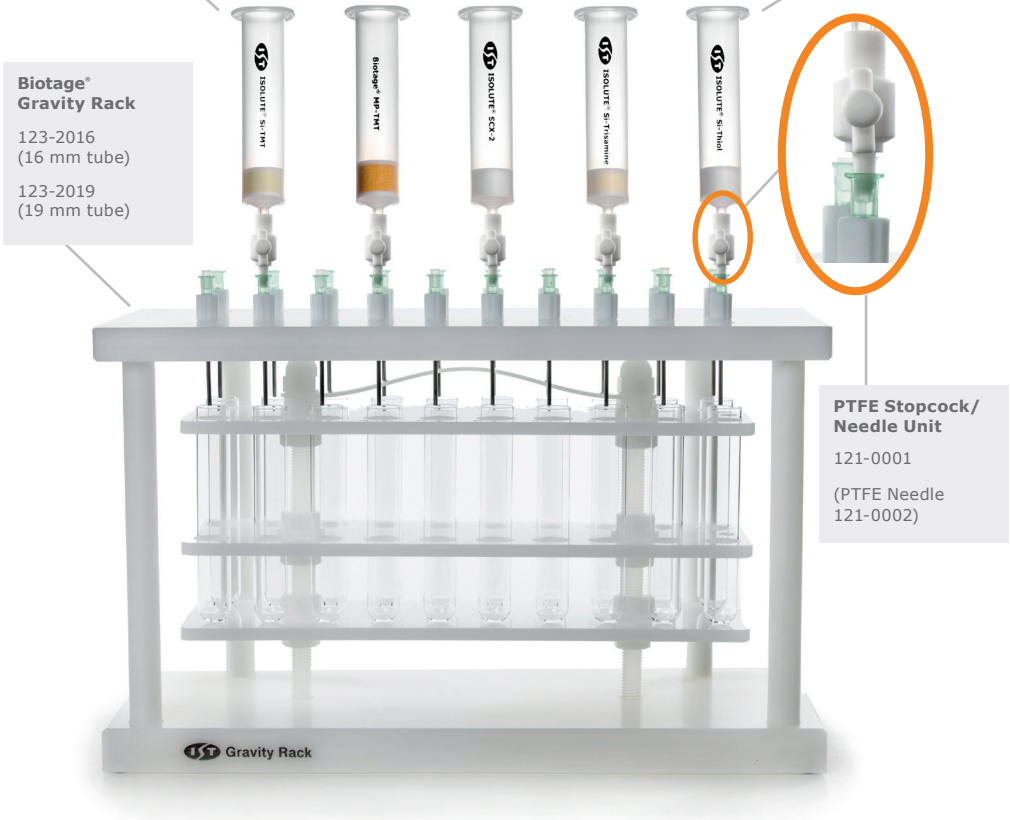
**Bulk Metal Scavengers: ISOLUTE® Si-Trisamine**
9495-0010 (10 g)
9495-0025 (25 g)
9495-0100 (100 g)
9495-1000 (1 Kg)

**Bulk Metal Scavengers: ISOLUTE® Si-Thiol**
9180-0010 (10 g)
9180-0025 (25 g)
9180-0100 (100 g)
9180-1000 (1 Kg)

**Biotage® Gravity Rack**

123-2016
(16 mm tube)

123-2019
(19 mm tube)

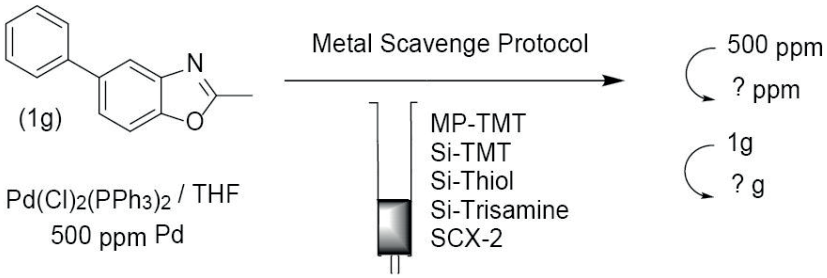



**PTFE Stopcock/ Needle Unit**

121-0001

(PTFE Needle 121-0002)

# Case Study: Worked Example of Metal Screening




## Experimental

10 mL of a 10 weight % benzoxazole (our model API analogue) solution containing 500 ppm Pd was passed through each of the 5 screening cartridges under gravity. Ethyl acetate (2 mL) was used to rinse each cartridge to remove residual solution, and the combined filtrate evaporated to dryness. The extract was weighed and analyzed for Pd content by ICP analysis.

## Results

### Part 1: Metal Screening

4 scavengers performed similarly (within single digit % point variation) [Si-TMT, MP-TMT, Si-Thiol, Si-Trisamine]. On paper Si-Trisamine would be the 'winner', and a scientist could easily proceed with Si-Trisamine based on this criteria, and expect to enjoy success in their application.

Assessing the data in the context of the overall workflow and risk analysis–may lead to consideration of alternate candidates to take forward. One of the goals of our study was to determine generic and robust methodologies, so even though Si-Trisamine came top, it is chemically basic, has risk of being 'switched-off' by competing ions or impurities, and uses a scavenging mechanism that is predominantly ionic. So its success; our scientists could tell was on a knife edge and potentially sensitive to variable change.

Si-TMT was chosen as our candidate metal scavenger due to its excellent all round performance and the fact that it is one of the core 3 (TMT or Thiol) scavengers which is inherently acid/base neutral–thus better to be employed as a generic method.

| Scavenger 1 g/15 mL Fixed Bed | Time to Flow Through/s | Vol. Flow Rate mL/min | Approx. Linear Flow Rate cm/min | Pd Before/ ppm | Pd After/ ppm | Mass Recovery/ % | Pd Reduction/ % |
|---|---|---|---|---|---|---|---|
| Biotage® MP-TMT | 333 | 1.8 | 1.4 | 500 | 10 | 99.3 | 98.0 |
| ISOLUTE® Si-TMT | 440 | 1.0 | 0.8 | 500 | 9 | 99.3 | 98.2 |
| ISOLUTE® Si-Thiol | 430 | 1.0 | 0.8 | 500 | 10 | 98.1 | 98.0 |
| ISOLUTE® Si-Trisamine | 371 | 1.4 | 1.0 | 500 | 9 | 99.8 | 98.2 |
| ISOLUTE® SCX-2 | 418 | 1.4 | 1.0 | 500 | 469 | 91.6* | 6.2 |
| Carbon | 380 | 1.6 | 1.2 | 500 | 94 | 66.0 | 81.2 |

*Mass recovery from strong cation exchanger ISOLUTE® SCX-2 cartridge was slightly lower than in the case of the other neutral or basic metal scavengers. Due to the nature of the Pd binding, ISOLUTE® SCX-2 is also not recommended in these cases, when the target molecule contains basic centers.

Additionally, the linear flow rate was on the low side, suggesting more residence time, more contact = better scavenging. Within experimental error, 9 ppm was left after Si-TMT, same as Si-Trisamine, so the **'real'** performance in this case, was similar. More significantly, the best scavenger results in terms of mass yields were within 0.5%, at screening stage, not really a decisive factor. We felt this was more instructive to eliminate larger deviation results, such as carbon, or SCX-2.

## Further Comments

In this screen, we also compared the Biotage metal scavengers with a classic carbon treatment. The carbon adsorption method removed some of the palladium but it was not the most effective. More significantly, significant amounts of our API analogue was lost to the carbon column (recovered yields were generally 66% compared to near quantitative from the metal scavengers).

**Part 2: Scale-up**

Based on initial screening results, the following parameters were chosen for further scale-up. The aspect ratio of the fixed bed was kept consistent with the 1 g/15 mL screening experiment.

- Metal Scavenger: ISOLUTE® Si-TMT
- Mass of Fixed-Bed: 50 g
- Dimensions: 80 mm x 40 mm (SNAP 50 g cartridge)
- Flow Mode: one pass
- Equilibration protocol: 3CV clean ethyl acetate
- Volumetric Flow rate: 15 mL/min
- Linear Flow Rate: 0.8 cm/min

| ISOLUTE® Si-TMT | Vol Flow Rate mL/min | Approx. Linear Flow Rate cm/min | Pd Before/ ppm | Pd After/ ppm | Pd Reduction/ % |
|---|---|---|---|---|---|
| 1 g/15 mL | 1.0 | 0.8 | 500 | 9 | 98.2 |
| 50 g Fixed Bed | 15 | 0.8 | 25000 | 95 | 99.6 |

## Summary/Conclusions

The metal scavenger kit was used to first screen a variety of metals against a compound chosen for inherent palladium chelation capacity, and also small drug-like molecular structure.

A candidate (ISOLUTE® Si-TMT) was taken forward and a fixed bed mimicking the aspect ratio and conditions of the screening experiment created. The reaction (representing a 50x fold scale increase) was passed through and palladium scavenging re-assessed.

In this worked example, the performance of ISOLUTE® Si-TMT in the screening experiment was indicative of subsequent performance during scale-up by the metal scavenger.

**Key Points:**

- Control major factors (which ones to control depends on the scavenging mechanism)
- Keep linear flow rates similar
- Any other limiting factors (other scavenging mechanisms)?
- Our project decision to use Si-TMT (not Si-Trisamine) worked well, as the scale-up scavenging efficiency improved slightly over the initial screen.

# Additional Factors to Consider

More advanced applications of metal scavenging may consider the following additional variables for optimization. For further information, please contact your local Biotage representative.

### Residence Time and Flow Rate

Depending on the mode of scavenging, it may be helpful to develop optimum flow rates for the desired scavenging interaction.

### Equivalents of Scavenger

A 1 g/15 mL Si-TMT cartridge will typically scavenge Pd from 1mol% catalyzed reactions run at 1–2 mmol scale. Once the scale of reaction is matched to the cartridge, the activity of various metal scavengers may be assessed.

### Temperature

Many scavenging process steps can be operated at RT in reasonable timescales (typically 15 min to 2 hr.). Faster rates of metal removal can be achieved by heating. Biotage media can withstand elevated temperatures without degradation and warm reaction mixtures and process streams may be channeled through fixed beds.

### pH of the Aqueous Reaction Mixtures

Biotage scavengers can be used across a wide pH range (pH 2–10), thought should be given to the optimum pH range for abstraction of a target metal or organic impurity. High pH (above pH 10) should generally be avoided with silica supported scavengers; resin based scavengers should be tested if it is necessary to work at this level of pH for extended periods of time.

### Other Reagents Present in the Reaction Mixture

Reactants that may be left in the reaction mixture may interact with the scavenger. Clearly there should be no interaction between the functional groups on the scavenger and the other reagents, otherwise this may necessitate the use of additional equivalents of the scavenger.

### Solvent

Macroporous resin (MP) and silica supported (Si) media can be used in a wide range of aqueous and organic solvents, including typical solvents such as THF, DMF, ethyl acetate, toluene, MeOH, ethers and chlorinated solvents. Co-solvent/ solvent substitution should be considered if kinetics are slow. Biotage has excellent support in advice in this respect.

## Batch/Flow

Silica scavengers are usually better in fixed bed applications, and resins are typically employed with batch stirring processes, however each scavenging situation is different and the reduced backpressure afforded by a fixed bed made of larger resin particles, may compensate for any differences in scavenging performance from one scavenger to another. It is important to consider overall process workflows in any evaluation. This kit contains a selection of both resin and silica based metal scavenger.

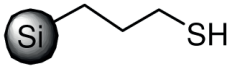
## Structure of the API

If the product or API of interest has a strong affinity for Pd, it will be necessary to use a more powerful metal scavenger to perform the optimization. In these cases, depending on the format (batch or flow) we would recommend using the MP-TMT or the Si-TMT scavengers.

# Technical Information and Specifications

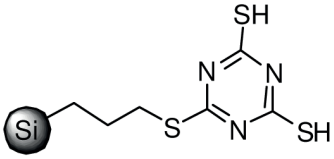
**ISOLUTE® Si-Thiol 1 g/15 mL Screening Cartridge (1.3mmol)**

ISOLUTE® Si-Thiol is the silica-bonded equivalent of 1-propanethiol, which is useful for covalent scavenging of electrophiles. The main application is the use to scavenge a variety of metals1,2 used in organic chemistry including Pd, Pt, Cu, Hg, Ag and Pb.



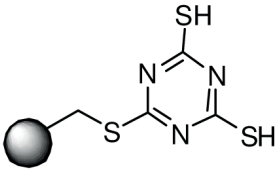

**ISOLUTE® Si-TMT 1 g/15 mL Screening Cartridge (0.3mmol)**

ISOLUTE® SI-TMT is the silica bound equivalent of 2,4,6-trimercaptotriazine (TMT). Si-TMT has been shown to efficiently scavenge residual palladium from palladium-catalyzed reactions.



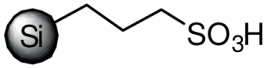

**Biotage® MP-TMT 1 g/15 mL Screening Cartridge (0.66mmol)**

Biotage® MP-TMT is a macroporous polystyrene-bound trimercaptotriazine, a resin bound equivalent of 2,4,6-trimercaptotriazine (TMT). MP-TMT scavenges residual palladium from palladium catalyzed reactions and has also shown to remove other metals. The MP-base co-polymer has been designed to yield a more robust, low swelling material, which makes it ideal for restricted volume environments. Its unique pore structure provides greater access to the reactive sites resulting in faster reactions and higher recoveries.



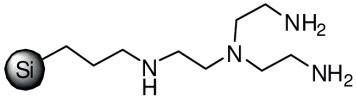
## ISOLUTE® SCX-2 (Si-Propylsulfonic Acid) 1 g/15 mL Screening Cartridge (0.7mmol)

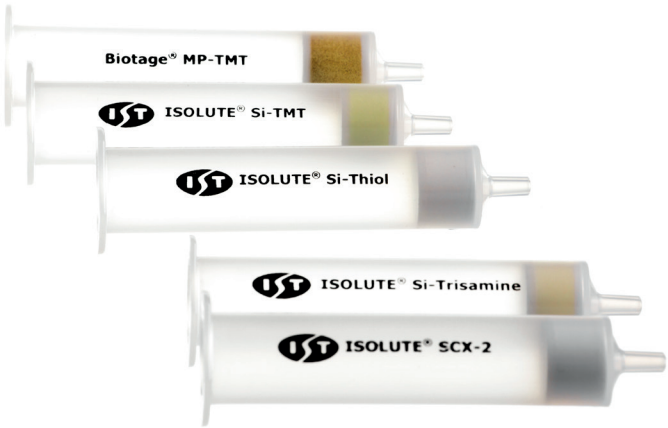
ISOLUTE® SCX-2 belongs to a class of silica materials which are strong acids. SCX-2 is a strong cation exchanger, and thus can be used in the scavenging of many alkaline metals, typically in +I oxidation states. Its strong acid character (pka 2–3) allows it to preferentially bind and retain basic components of reaction. This property may be leveraged in a chemical purification strategy, using a catch and release procedure.




## ISOLUTE® Si-Trisamine 1 g/15 mL Screening Cartridge (1.2mmol)

ISOLUTE® Si-Trisamine is a silica bound propyltris(2-aminoethyl)- amine. Si-Trisamine is a very powerful scavenger of electrophiles from aqueous or organic solutions as well as an effective scavenger for transition metals (+II oxidation states).



# Ordering Information

| Part Number | Description | Qty. |
|---|---|---|
| **K-MS-2** | Metal Scavenging Screening Kit (Batch Stir/Powder Format) | 1 |
| **801506** | Biotage® MP-TMT | 3 g |
| **801469** | Biotage® MP-TMT | 10 g |
| **801470** | Biotage® MP-TMT | 25 g |
| **801471** | Biotage® MP-TMT | 100 g |
| **801472** | Biotage® MP-TMT | 1 Kg |
| **9180-0010** | ISOLUTE® Si-Thiol | 10 g |
| **9180-0025** | ISOLUTE® Si-Thiol | 25 g |
| **9180-0100** | ISOLUTE® Si-Thiol | 100 g |
| **9180-0500** | ISOLUTE® Si-Thiol | 500 g |
| **9180-1000** | ISOLUTE® Si-Thiol | 1 Kg |
| **9538-0003** | ISOLUTE® Si-TMT | 3 g |
| **9538-0025** | ISOLUTE® Si-TMT | 25 g |
| **9538-0100** | ISOLUTE® Si-TMT | 100 g |
| **9538-1000** | ISOLUTE® Si-TMT | 1 Kg |
| **9495-0010** | ISOLUTE® Si-Trisamine | 10 g |
| **9495-0025** | ISOLUTE® Si-Trisamine | 25 g |
| **9495-0100** | ISOLUTE® Si-Trisamine | 100 g |
| **9495-1000** | ISOLUTE® Si-Trisamine | 1 Kg |
| **9536-0010** | ISOLUTE® Si-Propylsulfonic Acid (SCX-2) | 10 g |
| **9536-0025** | ISOLUTE® Si- Propylsulfonic Acid (SCX-2) | 25 g |
| **9536-0100** | ISOLUTE® Si- Propylsulfonic Acid (SCX-2) | 100 g |
| **9536-0500** | ISOLUTE® Si-Propylsulfonic Acid (SCX-2) | 500 g |
| **9536-1000** | ISOLUTE® Si- Propylsulfonic Acid (SCX-2) | 1 Kg |
| **Additional Cartridges** | | |
| **538-0050-C** | Si-TMT 500 mg/6 mL | 30/Pk |
| **180-0050-C** | Si-Thiol 500 mg/6 mL | 30/Pk |
| **Accessories** | | |
| **122-1025** | Biotage® FlashVac 10 Cartridge 25 mm collection tube Processing Manifold. | 1 |
| **123-2016** | Biotage® Gravity Rack 16 mm | 1 |
| **123-2019** | Biotage® Gravity Rack 19 mm | 1 |

For multi-kilogram quantities please contact your local Biotage representative.

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**Part Number: UI338**



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