## Drug Monograph

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| Drug/Drug Class: | **Mekinist® (trametinib) Tablet / Antineoplastic MEK Inhibitor** |
| Prepared for: | MO HealthNet |
| Prepared by: | Xerox Heritage, LLC |

☒ **New Criteria** ☐ **Revision of Existing Criteria**

## Executive Summary

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| **Purpose:** | The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use. |
| **Dosage Forms & Manufacturer:** | Mekinist® is available as 0.5mg and 2mg tablets containing 0.5 and 2mg of trametinib respectively.<br><br>GlaxoSmithKline Research Triangle Park, NC 27709 |
| **Summary of Findings:** | Mekinist has demonstrated efficacy by improving survival compared with chemotherapy in patients with unresectable or metastatic melanoma who have tested positive for BRAF V600E or V600K mutations. |
| **Status Recommendation:** | ☐ Prior Authorization (PA) Required ☒ Open Access<br>☐ Fiscal Edit ☐ PDL Product |
| **Type of PA Criteria:** | ☐ Increased Risk of ADE ☒ No PA Required<br>☐ Appropriate Indications ☐ 15 Day First Fill Fiscal Edit |

## Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

## Introduction

Melanoma is less common than other skin cancers. However, it is much more dangerous if it is not found early. It causes the majority (75%) of deaths related to skin cancer. Worldwide, doctors diagnose about 160,000 new cases of melanoma yearly. About 48,000 melanoma related deaths occur worldwide per year and once it metastasizes the survival rate decreases dramatically.

## Dosage Form(s) [1]

Mekinist® is available as 0.5mg and 2mg tablets containing 0.5 and 2mg of trametinib respectively.

## Manufacturer

GlaxoSmithKline Research Triangle Park, NC 27709

## Indication(s) [1]

Mekinist is FDA approved for the treatment of unresectable or metastatic melanoma in patients who have tested positive for BRAF V600E or V600K mutations with an FDA-approved test, but who have not previously received BRAF inhibitor therapy.

## Clinical Efficacy[1-2] (mechanism of action/pharmacology, comparative efficacy)

**PHARMACOLOGY (1)**

Mekinist is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 activity. MEK proteins promote cellular proliferation. MEK1 and MEK2 are included in the BRAF pathway, which is constitutively activated by BRAF V600E tumor mutations. Mekinish inhibits BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

**Pharmacokinetics (1)**

| | MEKINIST |
|---|---|
| **PROTEIN BINDING** | 97.4% |
| **VOLUME OF DISTRIBUTION** | 214 L |
| **METABOLISM** | Deacetylation either alone, with mono-oxygenation, or with glucuronidation |
| **EXCRETION** | Feces, > 80% ; Urine, < 20% |
| **HALF-LIFE** | 3.9 TO 4.8 DAYS |

**EFFICACY (1,2)**

 

**SUMMARY**

The approval of Mekinist was primarily based upon a phase 3, randomized, open-label clinical trial involving 322 patients with unresectable or metastatic melanoma. Mekinist significantly improved both progression-free survival (PFS) and 6-month overall survival (OS) compared with chemotherapy.

**UNRESECTABLE OR METASTATIC MELANOMA**

**CONCLUSION (1,2)**

Treatment with Mekinist significantly improved PFS and 6-month OS compared with chemotherapy in patients with unresectable metastatic melanoma.

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| **STUDY DESIGN** | Randomized, open-label, phase 3 clinical trial (n=322). |
| **INCLUSION CRITERIA** | Histologically confirmed unresectable stage IIIC or stage IV cutaneous (including patients with brain metastases at baseline) V600E (n=281) or V600K (n=40) BRAF-mutated melanoma. |
| **EXCLUSION CRITERIA** | More than one previous chemotherapy regimen for advanced or metastatic melanoma; any previous therapy with BRAF or MEK inhibitors or ipilimumab. |
| **TREATMENT REGIMEN** | Patients were randomized to receive either Mekinist 2 mg orally once daily (n=214; median age, 55 years; range, 23 to 85 years) or chemotherapy every 3 weeks (n=108; median age, 54 years; range, 21 to 77 years) that included either dacarbazine 1000 mg/m(2) IV or paclitaxel 175 mg/m(2) IV. Treatment continued until disease progression, death, or study withdrawal. If disease progression was confirmed by independent review, patients in the chemotherapy group were allowed to crossover to receive Mekinist. |
| **RESULTS** | Median PFS (intent-to-treat (ITT) population), the primary endpoint, was 4.8 months in the Mekinist group compared with 1.5 months in the chemotherapy group (hazard ratio (HR), 0.45; 95% CI, 0.33 to 0.63; $p < 0.001$). At 6 months, the OS (ITT) was 81% and 67% in the Mekinist and chemotherapy groups, respectively, despite crossover (HR of death, 0.54; 95% CI, 0.32 to 0.92; p=0.01). PFS results were similar in the primary efficacy population, which was amended to include only patients with V600E BRAF mutations without brain metastases at baseline (HR, 0.44; 95% CI, 0.31 to 0.64). The site investigator-confirmed response rate using Response Evaluation Criteria<br>in Solid Tumors (RECIST) criteria of complete or partial response occurred in 22% in the Mekinist group and in 8% in the chemotherapy group (p=0.01). The median duration of response was 5.5 months (95% CI, 4.1 to 5.9 months) in 47 patients in the Mekinist arm and had not been reached in the chemotherapy arm (n=9). |
| **SAFETY** | Commonly reported adverse events in the Mekinist group included rash, diarrhea, peripheral edema, and dermatitis acneiform; there were no reported cases of squamous cell carcinoma or hyperproliferative skin lesions. Serious grade 3 cardiac-related events leading to permanent discontinuation of Mekinist therapy occurred in 2 patients; decreased ejection fraction or ventricular dysfunction occurred in 7% of Mekinist patients. |

 

## Contraindications[1]

- None

## Warnings and Precautions[1]

- Cardiomyopathy (ie, cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction has been reported; monitoring recommended; therapy interruption may be necessary; discontinue permanently for symptomatic cardiomyopathy or asymptomatic cardiomyopathy that persists in spite of therapy interruption.
- Pregnancy; may cause fetal harm.
- Pulmonary toxicity, including interstitial lung disease (ILD) and pneumonitis, has been reported; interrupt therapy in patients with new or worsening pulmonary symptoms; discontinue permanently if ILD or pneumonitis is diagnosed.
- Retinal pigment epithelial detachments, typically bilateral and multifocal, have occurred; dose reduction, therapy interruption, and discontinuation may be necessary.
- Retinal vein occlusion (RVO) has been reported; discontinue use if RVO is diagnosed.
- Skin toxicity, serious and possibly requiring hospitalization, has been reported; may include rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, or erythema; monitoring recommended; dose reduction, therapy interruption, and discontinuation may be necessary.

## Adverse Effects[1]

| **Most common, >= 10%** | **Mekinist (n=211)** | | **Dacarbazine or Paclitaxel (n=99)** | |
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| | **All Grades** | **Grades 3 and 4** | **All Grades** | **Grades 3 and 4** |
| AST increased | 60% | 2% | 16% | 1% |
| Rash | 57% | 8% | 10% | 0% |
| Diarrhea | 43% | 0% | 16% | 2% |
| Hypoalbuminemia | 42% | 2% | 23% | 1% |
| ALT increased | 39% | 3% | 20% | 3% |
| Anemia | 38% | 2% | 26% | 3% |
| Lymphedema | 32% | 1% | 4% | 0% |
| Alkaline phosphatase increased | 24% | 2% | 18% | 3% |
| Dermatitis acneiform | 19% | < 1% | 1% | 0% |
| Hypertension | 15% | 12% | 7% | 3% |
| Stomatitis | 15% | 2% | 2% | 0% |
| Abdominal pain | 13% | 1% | 5% | 1% |
| Hemorrhage | 13% | < 1% | 0% | 0% |
| Dry skin | 11% | 0% | 0% | 0% |
| Paronychia | 10% | 0% | 1% | 0% |
| Pruritus | 10% | 2% | 1% | 0% |

 

## Drug Interactions[1]

No drug interaction studies have been conducted.

## Dosage and Administration[1]

The recommended dose is 2 mg orally once daily, taken 1 hour before or 2 hours after a meal, until disease progression or unacceptable toxicity. Dose adjustments are necessary for cutaneous, cardiac, ocular, or other Grade 3 or 4 adverse events.

## Cost Comparisons (at commonly used dosages)

| GENERIC NAME | BRAND NAME | MANUFACTURER | STRENGTH | DOSE | COST/ MONTH |
|---|---|---|---|---|---|
| Trametinib dimethyl sulfoxide | Mekinist | GlaxoSmithKline | 0.5 mg tablets | 2 tablets daily | $ 4489.20 ** |
| | | | 2 mg tablets | 1 tablet daily | $ 8978.40** |
| Dabrafenib mesylate | Tafinlar | GlaxoSmithKline | 50 mg capsules | 100 mg twice daily | $ 5067.60** |
| | | | 75 mg capsules | 150 mg twice daily | $ 7843.20** |
| Vemurafenib | Zelboraf | Genentech | 240 mg tablets | 960 mg twice daily | $ 5599.20** |

**Missouri Maximum Allowable Cost (MMAC)

## Conclusion

Mekinist has demonstrated efficacy by improving survival compared with chemotherapy in patients with unresectable or metastatic melanoma who have tested positive for BRAF V600E or V600K mutations. Mekinist is an oral MEK inhibitor, which differs mechanistically from the other oral agents available for the treatment of melanoma, which are BRAF inhibitors. Mekinist is not indicated in patients who have received previous BRAF inhibitor therapy. The most common adverse reactions are rash, diarrhea, peripheral edema, and dermatitis acneiform, while serious adverse reactions include cardiac, pulmonary, ocular, and cutaneous toxicities.

## Recommendation

The Division recommends open access status for this product.

## References

1. Product Information: Mekinist™, trametinib tablets. GlaxoSmithKline, Research Triangle Park, NC, 05/2013.

2. Flaherty KT, Robert C, Hersey P et al: Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012; 367(2):107-114.

 

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