Payers may require prior authorization or supporting documentation to process and cover a claim for the requested therapy. A prior authorization allows the payer to review the reason for the requested therapy and to determine medical appropriateness. The following are sample discussion points for a formulary exception letter that should be customized based on your patient's medical history and physical examination. They may also be used to explain why an insulin tolerance test (ITT) may not be medically appropriate for your patient. Please note that some payers may have specific forms that must be completed to request a formulary exception, prior authorization or to document medical necessity.

Please see Important Safety Information on the last page of this document.

Macrilen Medical Necessity Talking Points and Insulin Tolerance Test Concerns

If a payer requests that an Insulin Tolerance Test (ITT) be used in place of Macrilen, you may be able to appeal that decision. Below are sample talking points that may help to support your medical decision to use Macrilen.

- Any letter of medical necessity sent to a payer should include the patient's name, policy and group number, and diagnosis.
- The letter should be submitted on office letterhead and provide contact information for the physician.

Introduction, Product Summary, and Formal Request

- I am writing to request coverage for stimulation testing with Macrilen™ (macimorelin) for [Patient Name]. [Patient Name] has been under my care for [X months] for the treatment of [disease or symptoms].
- Provide a brief medical history, attach clinical records documenting that hormone deficiency is a result of hypothalamic-pituitary disease from organic or known causes (e.g., damage from surgery, cranial irradiation, head trauma, or subarachnoid hemorrhage), and/or document previously failed evocative AGHD stimulation tests.
- Macrilen (macimorelin) oral solution is a synthetic growth hormone secretagogue receptor agonist. It is a prescription drug that has been granted orphan drug designation in the U.S. and is the only FDA-approved (December 2017) oral growth hormone secretagogue receptor agonist indicated for the diagnosis of adult growth hormone deficiency (AGHD).

Contraindications, Limitations, and Caveats to ITT[1]: (Sample Discussion Points)

- The ITT stimulation test is contraindicated in several adult populations, including people with seizure disorders, those over the age of 65 years, patients with cardiovascular disease, and pregnant women.
- The ITT requires induction of a hypoglycemic state to reliably identify adult growth hormone deficiency. It requires ongoing monitoring for hypoglycemia to ensure that the desired state is achieved and then to guard against hypoglycemia-related adverse events, including neuroglycopenic events such as seizures and loss of consciousness.

[1] Yuen KCJ, et al. *Endoc Pract.* 2016;22:1235-44

- Add other statements to explain contraindications to ITT specific to your patient.

Adverse Events Related to ITT: (Sample Discussion Points)

- In addition to serious hypoglycemic events, adverse events – often severe—occurring in >10% of patients who participated in a large phase 3 trial (the 053 study) include sweating (67%), somnolence (36%), hunger (29%), dizziness (27%), asthenia (muscle weakness) (19%), nausea (13%), and palpitations (11%).[2]
    - Ultimately, the test is complicated for the clinician and burdensome for the patient, requiring canula insertion in both forearms and frequent blood draws, first to ensure that the desired hypoglycemic state has been achieved, and then to measure GH response
- Given these safety concerns, the ITT requires hospitalization, electrocardiogram monitoring, the presence of a crash cart, and continued monitoring after test completion until blood glucose returns to the normal range.[3]
- Add other statements to explain ITT adverse events specific to your patient.

Test Evaluability[2]: (Sample Discussion Points)

- ITT results are not highly reproducible, test results are often (~20% of the time) not evaluable.
- In the clinical trial, which compared Macrilen to the ITT, the Macrilen test was more evaluable than the insulin tolerance test.
    - 153 of 154 (>99%) Macrilen tests were evaluable upon first try.
    - 130 of 157 (83%) insulin tolerance tests were evaluable upon first try; about half of these were successfully evaluated with repeat testing
- Add other statements to explain test evaluability specific to your patient.

Conclusion

- I am a board-certified endocrinologist, and I believe that Macrilen is an appropriate agent for stimulation testing in the diagnosis of AGHD in this patient. It is imperative that a formulary exception be made.
- In my clinical judgement, diagnosing AGHD with Macrilen stimulation testing is medically necessary because of the product's diagnostic accuracy, safety profile, and labeled indication.
- Discuss rationale for using Macrilen over other non-FDA approved tests like the insulin tolerance test or glucagon stimulation test, including clinical factors, time required to safely administer each test, number of blood draws, test accuracy and repeatability, and physician work required.

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[2] Garcia JM, et al. J Clin Endocrinol Metab. May 2018. DOI:10.1210/jc.2018-00665

[3] Glynn N, Agha A. *Int J Endocrinol*. 2012;2012:972617

Additional Document Recommendations

- For your immediate review, I have enclosed additional documentation that supports Macrilen as an appropriate evocative agent for adult growth hormone stimulation testing.
- Please consider coverage of Macrilen for my patient. If you have further questions, please feel free to call me at [telephone number] to discuss.
- Enclosures: Full Prescribing Information (additional suggested: include original Prior
  Authorization Form, Denial/EOB, patient medical history, additional supporting documents)

Important Safety Information for Macrilen

Indication
Macrilen is indicated for the diagnosis of adult growth hormone deficiency (AGHD).

Limitations of Use
The safety and diagnostic performance of Macrilen have not been established for subjects with a body mass index (BMI) > 40 kg/m^2.

Warnings and Precautions

QT Prolongation
Macrilen causes an increase of about 11 msec in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases. The concomitant use of Macrilen with drugs that are known to prolong the QT interval should be avoided.

Potential for False Positive Test Results with Use of Strong CYP3A4 Inducers
Concomitant use of strong CYP3A4 inducers with Macrilen can decrease macimorelin plasma levels significantly and **thereby lead to a false positive result**. **Strong CYP3A4 inducers should be discontinued and enough time should be given to allow washout** of **CYP3A4 inducers prior to test administration**.

Potential for False Negative Test Results in Recent Onset Hypothalamic Disease
Adult growth hormone (GH) deficiency caused by a hypothalamic lesion may not be detected early in the disease process. Macimorelin acts downstream from the hypothalamus and macimorelin stimulated release of stored GH reserves from the anterior pituitary could produce a false negative result early when the lesion involves the hypothalamus. Repeat testing may be warranted in this situation.

Adverse Reactions
The most common adverse reactions were dysgeusia, dizziness, headache, fatigue, nausea, hunger, diarrhea, upper respiratory tract infection, feeling hot, hyperhidrosis, nasopharyngitis, and sinus bradycardia.

Please see Full Prescribing Information**.**