BlueCross BlueShield Nebraska

JYNARQUE (REQUIRES PREAUTHORIZATION)

X.130

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OBJECTIVE

The intent of the Jynarque prior authorization with quantity limit program is to encourage appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. The program will not be approved for those who have any FDA labeled contraindication to the requested agent. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis. Requests will be reviewed when patient specific documentation is provided.

Dates

Original Effective
05-30-2018
Last Review
11-06-2024
Next Review
11-12-2025

POLICY

1. The patient has a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) confirmed by ONE of the following:

OR

c. Genetic testing

AND

2. ONE of the following:
   a. The patients has had a sequential increase of >5% annually in TKV on imaging

      OR

   b. Total kidney volume (TKV) >750 mL

      OR

   c. Kidney length (KL) >16.5 cm

      OR

   d. The patient has typical (Class 1) ADPKD and ONE of the following:
      i. The patient has been classified as 1C, 1D, or 1E using the Mayo ADPKD Classification assessment

      OR

      ii. The prescriber has provided documentation indicating the patient's ADPKD is rapidly progressing

      OR

   e. The patient has atypical (Class 2) ADPKD and the prescriber has provided documentation indicating the patient's ADPKD is rapidly progressing

   AND

3. ONE of the following:
   a. The patient is initiating therapy and ONE of the following:
      i. The patient's ALT, AST, bilirubin has been measured within the past 3 months prior to initiating therapy with the requested agent AND ONE of the following:
         1. The patient's most recent ALT, AST, and bilirubin levels are under the upper limit of normal (ULN)

            OR

         2. The patient's most recent ALT, AST, and bilirubin levels are above the ULN and the prescriber has provided documentation in support of use with the requested agent with the elevated levels

            OR

the past 3 months AND ONE of the following:

1. The patient's most recent levels have NOT exceeded EITHER of the following:
   a. ALT or AST 2 times ULN
      OR
   b. ALT or AST 2 times the patient's baseline prior to initiating therapy with the requested agent
      OR
2. BOTH of the following:
   a. The most recent ALT or AST levels have exceeded 2 times ULN or 2 times the patient's baseline prior to initiating therapy with the requested agent
      AND
   b. The prescriber has provided documentation in support of use with the requested agent while at these elevated levels
      AND

ii. ONE of the following:

1. The patient has never experienced ALT or AST levels exceeding 3 times ULN while on therapy with the requested agent
   OR
2. BOTH of the following:
   a. The prescriber has provided documentation indicating that the ALT or AST levels exceeding 3 times ULN while on therapy with the requested agent were due to cause unrelated to therapy with the requested agent
      AND
   b. The patient's current ALT and AST levels have stabilized and are now below 3 times ULN
      AND

4. The patient will continue to receive routine ALT, AST, and bilirubin monitoring at least every 3 months
   AND
5. ONE of the following:

b. The other tolvaptan agent will be discontinued prior to starting therapy with the requested agent

AND

6. The prescriber is a specialist (e.g. nephrologist) or has consulted with a specialist in the area of the patient's diagnosis

AND

7. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

8. ONE of the following:

a. The requested quantity (dose) is NOT greater than the program quantity limit

OR

b. ALL of the following:

i. The requested quantity is greater than the program quantity limit

AND

ii. The requested quantity (dose) is less than or equal to the maximum FDA labeled dose

AND

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

Length of Approval: 12 months

Renewal Evaluation

AND

2. The prescriber has indicated that the patient has received benefit from the requested agent

AND

3. The patient has had ALT, AST, and bilirubin assessed in the past 3 months AND ONE of the following:
   a. The patient's most recent levels have NOT exceeded EITHER of the following:
      i. ALT or AST 2 times ULN

      OR

      ii. ALT or AST 2 times the patient's baseline prior to initiating therapy with the requested agent

      OR

   b. BOTH of the following:
      i. The most recent ALT or AST levels have exceeded 2 times ULN or 2 times the patient's baseline prior to initiating therapy with the requested agent

      AND

      ii. The prescriber has provided documentation in support of use with the requested agent while at these elevated levels

      AND

4. ONE of the following:
   a. The patient has never experienced ALT or AST levels exceeding 3 times ULN while on therapy with the requested agent

   OR

   b. BOTH of the following:
      i. The prescriber has provided documentation indicating that the ALT or AST levels exceeding 3 times ULN while on therapy with the requested agent were due to cause unrelated to therapy with the requested agent

      AND

      ii. The patient's current ALT and AST levels have stabilized and are now below 3 times ULN

      AND

5. The patient will continue to receive routine ALT, AST, and bilirubin monitoring at least every 3 months

tolvaptan agent

OR

b. The other tolvaptan agent will be discontinued prior to starting therapy with the requested agent

AND

7. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

8. ONE of the following:

a. The requested quantity (dose) is NOT greater than the program quantity limit

OR

b. ALL of the following:

i. The requested quantity is greater than the program quantity limit

AND

ii. The requested quantity (dose) is less than or equal to the maximum FDA labeled dose

AND

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

Length of Approval: 12 months

CLINICAL RATIONALE

Autosomal dominant polycystic kidney disease (ADPKD) occurs in approximately 1 in every 400 to 1000 live births. It is estimated that less than half of the cases will be diagnosed since the disease is often clinically silent. PKD1 is related to an abnormality on chromosome 16. PKD2 is related to a defect on chromosome 4. In approximately 8% of families with ADPKD, no mutations are detected at these chromosomes.[1]

- For asymptomatic individuals, renal ultrasonography is usually used for screening because it is safe, effective, and inexpensive. Criteria for diagnosis varies depending upon whether the familial genotype is known:
  - For at risk individuals with unknown family genotype, diagnosis is based on the following:
    - Among individuals between 15 and 39 years of age, at least three unilateral or bilateral kidney cysts.
    - Among individuals 40 to 59 years of age, at least two cysts in each kidney.
    - Among individuals 60 years or older, at least four cysts in each kidney.
  - For individuals at risk for PKD1 due to family history, genetic testing may be more definitive. The following ultrasonography criteria may also be used for diagnosis:
    - Among individuals between 15 and 30 years of age, at least two unilateral or bilateral cysts
    - Among individuals 30 to 59 years of age, two cysts in each kidney
    - Among individuals 60 years or older, four cysts in each kidney
  - For individuals at risk for PKD2 due to family history, genetic testing may be more definitive. Otherwise, diagnosis criteria through ultrasonography for individuals with unknown genotype is used.
- For patients with symptomatic disease who have a family history of ADPKD, the diagnosis is certain with the finding of large kidneys with multiple bilateral cysts on ultrasonography or CT scanning
  - The specific number of cysts per kidney detected by ultrasonography that will definitively establish the diagnosis of ADPKD depends upon patient age and is the same as the criteria used in patients with asymptomatic disease

than ultrasound, diagnosis criteria for ultrasound results do not apply to CT and MRI scans.

- Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference[3]
  - Asymptomatic at risk patients
    - Ultrasonography is most commonly used for diagnosis
      - Total of ≥3 renal cysts subjects aged 15-39 years
      - ≥2 renal cysts in each kidney subjects aged 40-59 years
    - MRI or CT may also be used
      - Total of <5 renal cysts is sufficient for disease exclusion
- American Academy of Family Physicians[4]
  - Ultrasonography for at risk ADPKD type 1
    - ≥2 cysts in one kidney or both kidneys for those <30 years of age
    - ≥2 cysts in each kidney for those 30-59 years of age
    - ≥4 cysts in each kidney for those ≥60 years of age
  - Ultrasonography for those at risk and unknown genotype
    - ≥3 cysts in one or both kidneys for those 15-39 years of age
    - ≥2 cysts in each kidney for those 40-59 years of age
    - ≥4 cysts for those ≥60 years of age
  - MRI for those at risk
    - ≥5 cysts in each kidney for those <30 years of age
    - ≥6 cysts in each kidney for those 30-44 years of age
    - >6 cysts in each kidney for females 45-59 years of age
    - >9 cysts in each kidney for males 45-59 years of age

A Canadian expert consensus recommends the following for assessing individuals for the targeting treatment:[7]

- Patients should be referred to a nephrologist for initial assessment
- Recommend that before quantifying the size of the kidneys, patients should be classified according to the Mayo Clinic classification for typical (Class 1) versus atypical (Class 2) morphology with renal imaging.

candidates to be considered for therapeutic intervention based on their risk of progression.

- Recommend the use of ellipsoid TKV or ultrasound (US) to determine TKV in routine clinical practice, although the gold standard for measuring total kidney volume (TKV) is MRI stereology.
- Suggest that MRI or CT height adjusted total kidney volume (htTKV) is currently the most accurate method of assessing renal size in patients with ADPKD.
- In the absence of MRI, imaging by CT may be used to determine TKV. In situations where an MRI or CT is not easily obtainable, suggest using US-measured kidney length (KL) as a suitable surrogate. US can be used to determine TKV; however, TKV obtained using US may introduce error and does not provide an advantage over KL.
- Recommend that routine assessment of TKV or KL should not exceed a frequency of once yearly.
- Recommend that in current clinical practice, patients with a TKV measurement be categorized in terms of their risk of progression as per the Mayo Clinic classification or other validated clinical tools (e.g. PROPKD score, genetic scoring). The application of the Mayo Classification to clinical practice has not yet been delineated; however, it appears to be the most robust clinical prediction tool as it pertains to the important marker of htTKV.
- Currently available TKV-based prognostication tools should not be applied to class 2 (atypical morphology) patients. Suggest that these patients are unlikely to be rapid progressors. Certain patients may require further clinical evaluation.
- Suggest that patients who are classified as Mayo class 1C, D, or E be considered to be at risk of rapid progression of their ADPKD renal disease.
- Recommend that patients who demonstrate a sequential increase of >5% annually in TKV on imaging should be considered at risk of rapid progression of their ADPKD-related renal disease.
- Recommend that patients with an US KL of >16.5 cm bilaterally should be considered at high risk of progression of

assessment is needed.

- Suggest that baseline TKV and KL are important determinants of renal progression of ADPKD; however, serial TKV and KL measurements have not been established as markers to monitor response to therapy
- Recommend treatment with tolvaptan for patients who fulfill the enrollment criteria of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 study:
  - 18 to 50 years of age
  - Cockcroft-Gault GFR >60 mL/min. In the absence of Cockcroft-Gault GFR, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) >45 mL/min may be used
  - And TKV >750 mL. In the absence of TKV, ultrasound (US) kidney length (KL) >16.5 cm may be used
- Suggest treatment with tolvaptan for patients who, according to the Mayo Classification, are classified as 1D or 1E with eGFR in CKD stage 3 or higher. Treatment with tolvaptan should be considered for patients who are classified as 1C and are younger than 50 years or have other risk factors for rapid progression

Safety

Jynarque has the following black box warnings:[1]

- Jynarque can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported
- Measure transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter
- Jynarque is available only through a restricted distribution program called the Jynarque REMS Program

Jynarque has the following contraindications:[1]

- History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease
- Concomitant use of strong CYP 3A inhibitors is contraindicated

- Hypersensitivity to tolvaptan or any of its components
- Uncorrected urinary outflow obstruction
- Anuria

Jynarque can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity.[1]

In a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan treated patients compared to none of the placebo treated patients.[1]

To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiation of Jynarque, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.[1]

At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue Jynarque, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, Jynarque may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times ULN.[1]

Do not restart Jynarque in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved.[1]

In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.[1]

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REVISIONS

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