BlueCross BlueShield of Alabama

Jynarque Prior Authorization with Quantity Limit Program Summary

This program applies to Blue Partner, Commercial, GenPlus, NetResults A series, SourceRx, and Health Insurance Marketplace.

Jynarque Prior Authorization with Quantity Limit

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.

TARGET AGENT(S)
Jynarque (tolvaptan)

PROGRAM PRIOR AUTHORIZATION AND QUANTITY LIMITS

Brand (generic)	GPI	Multisource Code	Quantity Limit
Jynarque (tolvaptan)			
45 mg / 15 mg blister card	3045406000B725	M, N, O, Y	56 tablets (4 blister cards) / 28 days;
60 mg / 30 mg blister card	3045406000B735	M, N, O, Y	56 tablets (4 blister cards) / 28 days
90 mg / 30 mg blister card	3045406000B745	M, N, O, Y	56 tablets (4 blister cards) / 28 days

PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL
Jynarque will be approved when ALL of the following are met:
Initial Evaluation

1. The patient has a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) confirmed by ONE of the following:
   a. Ultrasonography
      OR
   b. MRI or CT scan
      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

    b. The patient is continuing therapy and BOTH of the following:
        i. The patient has had ALT, AST, and bilirubin assessed in 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:
   a. The patient is not currently on therapy with another tolvaptan agent

      OR

   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

1. The patient has been previously approved for the requested agent through Prime Therapeutics Prior Authorization Review process

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

AND

6. ONE of the following:
    a. The patient is not currently on therapy with another 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

FDA APPROVED INDICATIONS AND DOSAGE[1]

<table>
<tr><th>Agent</th><th>Indication</th><th>Dosage & Administration</th></tr>
<tr><td>Jynarque™
(tolvaptan)

Tablet</td><td>To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)</td><td>Recommended dosage:
<table>
<tr><th>Initial Dosage</th><th>Titration Step</th><th>Target Dosage</th></tr>
<tr><td>1st dose: 45 mg</td><td>1st dose: 60 mg</td><td>1st dose: 90 mg</td></tr>
<tr><td>2nd dose (8 hours later): 15 mg</td><td>2nd dose (8 hours later): 30 mg</td><td>2nd dose (8 hours later): 30 mg</td></tr>
<tr><td>Total daily dose: 60 mg</td><td>Total daily dose: 90 mg</td><td>Total daily dose: 120 mg</td></tr>
</table></td></tr>
</table>

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]

A consensus diagnosis algorithm for ADPKD is not available. Multiple guidelines offer similar yet different diagnostic criteria:

- UptoDate[2]
    - 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
        - Ultrasound results may be equivocal, in which case, CT or MRI scans or genetic testing may help determine diagnosis. Because CT and MRI scans are more sensitive 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.
- Recommend that a baseline assessment of renal size be undertaken in patients with ADPKD. The objective of these measurements is to determine which patients are suitable 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 their ADPKD-related renal disease. A KL >16.5 cm has been shown to correlate with a TKV of 750 mL; however, direct measurement of TKV would be required if more accurate 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

Efficacy

Tolvaptan was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages.[5,6]

TEMPO 3:4 was a phase 3, double-blind, placebo-controlled, randomized trial which included 1445 adult patients (age >18 years) with early (estimated creatinine clearance [eCrCl] ≥60 mL/min), rapidly-progressing (total kidney volume [TKV] ≥750 mL and age <51 years) ADPKD (diagnosed by modified Ravine criteria). Patients were randomized 2:1 to treatment with tolvaptan or placebo. Patients were treated for up to 3 years;

patients who discontinued medication prematurely were only required to attend clinic visits to assess renal function for up to 42 days after treatment withdrawal and to attend telephone visits at all scheduled visits for up to 36 months. Patients who completed treatment at the 3-year visit had treatment interrupted for 2-6 weeks to assess renal function post treatment. Patients received treatment twice a day (first dose on waking, second dose approximately 9 hours later). Patients were initiated on 45 mg/15 mg, and up-titrated weekly to 60 mg/30 mg and then to 90 mg/30 mg as tolerated. Patients were to maintain the highest tolerated dose for 3 years, but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to drink adequate water to avoid thirst or dehydration and before bedtime.[5]

At baseline, average estimated glomerular filtration rate (eGFR) was 82 mL/min/1.73 m^2 (CKD-Epidemiology formula) and mean total kidney volume (TKV) was 1692 mL (height adjusted 972 mL/m). Approximately 35% had an eGFR of 90 mL/min/1.73 m^2 or greater, 48% had an eGFR between 60-89 mL/min/1.73 m^2, 14% had an eGFR of 45-60 mL/min/1.73 m^2, and 3% had an eGFR of <45 mL/min/1.73 m^2. The trial met its prespecified primary endpoint of 3-year change in TKV ($p<0.0001$). Over the 3-year period, TKV increased by 2.8% per year (95% confidence interval [CI], 2.5 to 3.1) with tolvaptan versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo. The difference in TKV between treatment groups mostly developed within the first year, the earliest assessment, with little further difference in years two and three. In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received tolvaptan and the difference between the groups in TKV was not maintained. Tolvaptan has little effect on kidney size beyond what accrues during the first year of treatment.[5]

The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; $p=0.0095$). As shown in the table below, the result of the key secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. Few subjects in either arm required a radiologic or surgical intervention for kidney pain. Most kidney pain events reflected use of a medication to treat pain such as use of paracetamol, tricyclic antidepressants, narcotics and other non-narcotic agents.[5]

Event	**Tolvaptan**		**Placebo**		**Hazard Ratio, 95% CI**
	Total Number of Events (Events per 100 person-years)	**Number of Subjects with an Event (percentage)**	**Total Number of Events (Events per 100 person-years)**	**Number of Subjects with an Event (percentage)**	
Composite	1049 (43.9)	572 (59.5)	665 (50.0)	341 (70.6)	0.87 (0.78,0.97)
Worsening Kidney Function	44 (1.9)	42 (4.6)	64 (4.8)	61 (12.8)	0.39 (0.26,0.57)
Kidney Pain	113 (4.7)	95 (9.9)	97 (7.3)	78 (16.2)	0.64 (0.47,0.89)

Event	Tolvaptan		Placebo		Hazard Ratio, 95% CI
	Total Number of Events (Events per 100 person-years)	Number of Subjects with an Event (percentage)	Total Number of Events (Events per 100 person-years)	Number of Subjects with an Event (percentage)	
Onset or progression of hypertension	734 (30.7)	426 (44.3)	426 (32.1)	244 (50.5)	0.94 (0.81,1.09)
Worsening Albuminuria	195 (8.2)	195 (20.3)	103 (7.8)	101 (20.9)	1.04 (0.84,1.28)

The third endpoint (kidney function slope) was assessed as slope of eGFR during treatment (from end of titration to last on-drug visit). The estimated difference in the annual rate of change in those who contributed to the analysis was 1.0 mL/min/1.73 m^2/year with a 95% confidence interval of (0.6, 1.4). Of the subjects enrolled in the trial, 5% of subjects in the tolvaptan arm and 2% in the placebo arm either had missing baseline data or discontinued from treatment prior to the end of the titration visit and hence were excluded from the analysis. In the extension trial, eGFR differences produced by the third year of the TEMPO 3:4 trial were maintained over the next 2 years of tolvaptan treatment.[5]

REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56; or eGFR between 25 and 44 mL/min/1.73 m^2, plus eGFR decline >2.0 mL/min/1.73 m^2/year if between age 56-65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-week follow-up period to assess renal function.[6]

Prior to randomization, patients were required to complete sequential single-blind run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. During the titration period, tolvaptan was up-titrated every 3-4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo.[6]

Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration.
A total of 1313 subjects were included in the primary efficacy analysis.[6]

For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m^2 (CKD-Epidemiology formula) and historical TKV,

available in 318 (23%) of subjects, averaged 2026 mL. Approximately 5%, 75% and 20% had an eGFR 60 mL/min/1.73 m or greater, between 30-59 mL/min/1.73 m^2, and between 25 and 29 mL/min/1.73 m^2, respectively. Of the 115 (8%) of subjects who had prior genetic tests, only 54 (47%) knew their results with 48 (89%) of these having PKD1 and 6 (11%) having PKD2 mutations.[6]

In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was –2.3 mL/min/1.73 m^2/year with tolvaptan as compared with –3.6 mL/min/1.73 m^2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m^2/year (p <0.0001). The key secondary endpoint (eGFR slope in ml/min/1.73 m^2/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 ml/min/m^2/year that was also statistically significant (p <0.0001).[6]

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
- Uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- 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]

REFERENCES

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