

# PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No. 4 November 2011

*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

## Recommendation of periodic liver function tests and monitoring of signs/symptoms for patients treated with the gout/hyperuricaemia treatment benzbromarone

Hepatic disorder may occur as an adverse reaction associated with benzbromarone for gout/hyperuricaemia treatment. Continuous treatment despite signs of hepatic disorder has resulted in aggravation of symptom in some cases.

Please pay attention to the following precautions when using benzbromarone!!

- **Be sure to perform periodic liver function tests for at least the first 6 months of initial administration. Periodic tests are also recommended after the first 6 months!**
- **Healthcare professionals should advise patients that the patients should carefully note symptoms associated with hepatic disorder and immediately stop taking the drug and contact a healthcare professional if any symptoms occur!**
- **Patients should be carefully monitored for signs of hepatic disorder including abnormal test results or signs/symptoms during the treatment!**



Alerts against serious hepatic disorder associated with benzbromarone is included in the package insert. Dear Healthcare Professional Letters of Emergent Safety Communications were also issued in February 2000. However, about 20 cases of serious hepatic disorder are still reported every year. Hepatic disorder became serious in some cases in which no periodic liver function tests were performed or the treatment was continued despite abnormal liver function test results or associated signs/symptoms.

### Case summaries

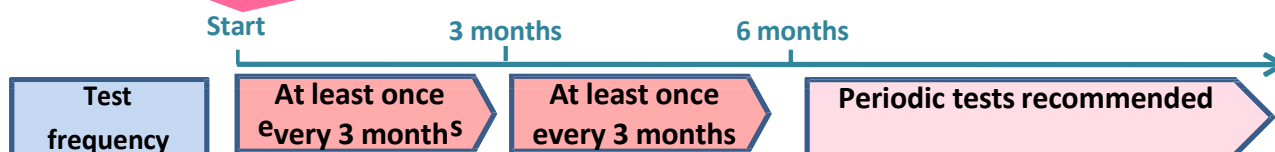
**(Case 1)** A male patient in his 50s. The patient started receiving benzbromarone 50 mg/day for the treatment of gout. On Day 29, the liver function test showed no abnormalities. On Day 128, the patient visited the hospital for general malaise, epigastric discomfort, and brown urine that had started 2 weeks earlier. Because of the elevated liver function test (AST 1315 U/L; ALT 1383 U/L;  $\gamma$ -GTP 701U/L), the patient was admitted to the hospital, and administration of benzbromarone was discontinued.

**(Case 2)** A female patient in her 70s. The patient started receiving benzbromarone 50 mg/day for the treatment of hyperuricaemia. On Day 111, AST, 57 U/L; ALT, 77 U/L and  $\gamma$ -GTP, 193 U/L. The patient had no symptoms, and the follow-up was continued. On Day 151, AST 145 U/L; ALT 161U/L and  $\gamma$ -GTP 95 U/L. On Day 165, the patient developed slight fever, malaise, and anorexia. On Day 175, administration of benzbromarone was discontinued, and the patient was admitted to the hospital because of the elevated liver function test (AST 291 U/L; ALT 355 U/L;  $\gamma$ -GTP 254 U/L) and jaundice.

**Ⓞ Perform liver function tests at the following intervals, and patients should be carefully monitored for signs and symptoms.**

Periodic liver function tests must be performed at least for the first 6 months of the initial administration (about at least once every 3 months) . The periodic tests are also recommended after the first 6 months.

Pre-treatment test!  
Contraindicated in patients with hepatic disorder



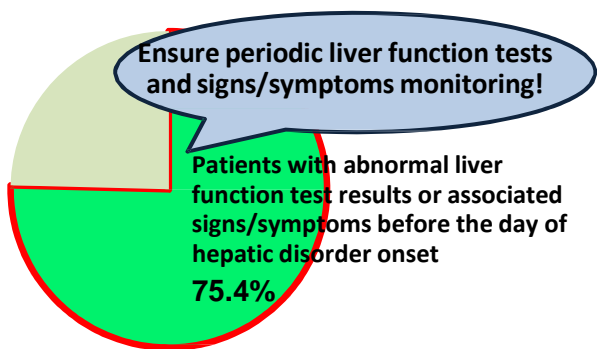
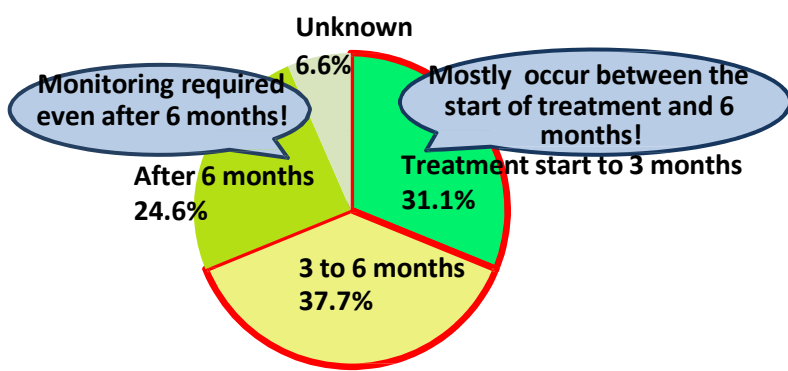
Signs and symptoms: Patients should be closely observed for signs and symptoms.

Ex. anorexia, nausea/vomiting, general malaise, abdominal pain, diarrhea, pyrexia, dark urine, jaundice (yellowing of the white of eye and skin)

- Instruct the patient to discontinue administration of benzbromarone immediately and consult a physician if such symptoms occur.
- Discontinue administration of benzbromarone and take appropriate measures if the patient has abnormal liver function test results and experiences the signs/symptoms.

Time of onset of hepatic disorder <sup>Note 1)</sup>

Presence of signs before the day of hepatic disorder onset <sup>Note 1)</sup>



Note 1) Based on 61 cases of hepatic disorder associated with benzbromarone reported to the PMDA in and after 2008

See "WARNINGS" and "Important Precautions" sections of package insert for liver function tests and signs/symptoms monitoring.

According to the Relief System for Sufferers from Adverse Drug Reactions, the relief system is not applicable to improper use of drug, for example, in cases where appropriate liver function tests are not performed, resulting in aggravation of symptoms.

© Package insert; liver function tests and symptom/sign monitoring

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| <p><b>[WARNINGS]</b><br/>                 1. Serious hepatic disorders such as fulminant hepatitis have been reported, which mainly occur within first 6 months of initial administration and lead to serious outcomes such as death in some cases. Liver function tests should be periodically performed for at least the first 6 months after start of administration. Patients should be carefully monitored. If any abnormal liver function test results or jaundice are observed, administration of this drug should be discontinued, and appropriate measures should be taken.<br/><br/>                 2. Patients should be informed of possible hepatic disorder associated with this drug in advance. In addition, the patients should be advised to discontinue of this drug and immediately consult a physician if anorexia, nausea/vomiting, general malaise, abdominal pain, diarrhoea, pyrexia, dark urine, or conjunctiva bulbi colouring yellow are observed.</p> <p><b>[CONTRAINDICATIONS]</b> (Benzbromarone is contraindicated in the following patients)<br/>                 1. Patients with hepatic disorder (the existing hepatic disorder may be aggravated)</p> | <p><b>[PRECAUTIONS]</b><br/>                 1. Important Precautions<br/>                 (1) Liver function tests should be performed before start of administration and absence of hepatic disorder should be confirmed. (See “CONTRAINDICATIONS”.)<br/>                 (2) Serious liver dysfunction have been reported, which mainly occur within first 6 months of treatment with this drug. Liver function tests should be periodically performed for at least the first 6 months after initiation of administration. Also periodic liver function tests should be performed even after the 6 first months. (See “WARNINGS.”)<br/><br/>                 3. Adverse Reactions<br/>                 (1) Clinically significant adverse reactions<br/>                 Serious hepatic disorder (frequency unknown*): Serious hepatic disorder such as fulminant hepatitis and jaundice may occur. Patients should be carefully monitored through periodic liver function tests. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. (See “WARNINGS.”)<br/>                 *Frequency of spontaneously reported cases is unknown.</p> |
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As of November 2011

| <b>Product name of benzbromarone (Name of Marketing Authorization Holder)</b>  |  |
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| UROLEAP Tablets 50<br>(Taiyo Pharmaceutical Industry Co., Ltd.)<br>GOUTMALON Tab. 25 mg, 50 mg<br>(Kyowa Pharmaceutical Industry)<br>KIRANGA Tablets 25 mg, 50 mg (Isei Co., Inc.)<br>TREBIANOM TABLETS 25 mg, 50 mg<br>(Towa Pharmaceutical Co., Ltd.)<br>NARCARICIN Tab. 25 mg, 50 mg<br>(Nagase Medicals Co., Ltd.) | MUIRODINE FINE GRAN. 10%<br>(Kotobuki Pharmaceutical Co., Ltd.)<br>BENZMARONE Tablets 25 mg, 50 mg (Kyorin Rimedio Co., Ltd.)<br>Benzbromarone TAB. 25 mg “NICHIIKO”,<br>BROMANOME TAB. 50 mg<br>(Nichi-Iko Pharmaceutical Co., Ltd.)<br>URINORM Tab. 25 mg, 50 mg (Trii Pharmaceutical Co., Ltd.) |

As of November 2011

See information on the precautions related to benzbromarone, including hepatic disorder, at the Pharmaceuticals and Medical Devices Information website  
[http://www.info.pmda.go.jp/psearch/html/menu\\_tenpu\\_base.html](http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html) (in Japanese)

**About this information**

- \* “PMDA Alert for Proper Use of Drugs” communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the Pharmaceutical Affairs Law.
- \* We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future.
- \* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibilities on them, but is provided to promote the proper use of drugs.

