PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No. 5 December 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.

Periodic blood tests and symptom checks should be performed for prevention and early detection of agranulocytosis associated with the antithyroid drug thiamazole.

◎ Periodic blood test

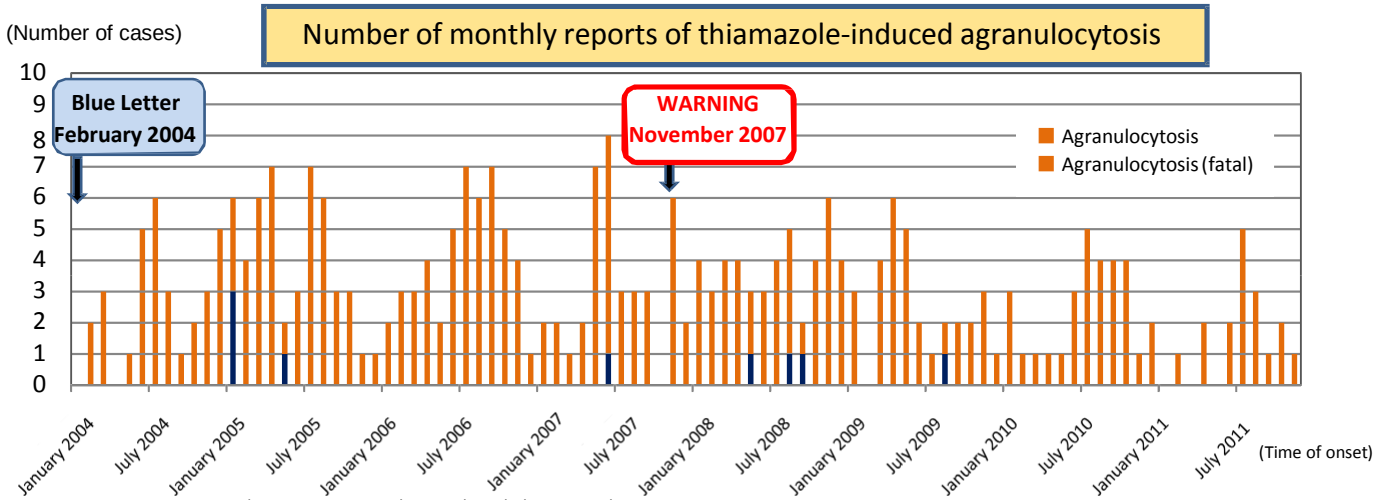
- **Healthcare professionals should perform periodic blood tests once every 2 weeks for at least first 2 months of initial administration. Blood tests should be periodically performed even of initial 2 months!**
- **Blood tests should include differential leukocyte count!**
- **If the white blood cell (WBC) count is within the normal range but decreasing, administration of thiamazole should be immediately discontinued, and appropriate measures should be taken!**

◎ Symptom check

Healthcare professionals should thoroughly instruct patients:

- **to consult their physician immediately if pharynx pain, pyrexia, and malaise occur, and**
- **to inform physicians of use of thiamazole when seeking medical attention!**

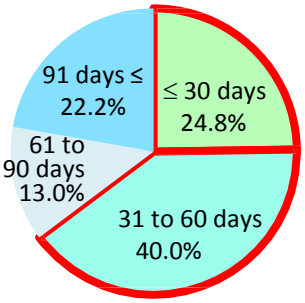
Alerts against thiamazole-induced agranulocytosis are included in Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) issued in February 2004 and the WARNINGS section of package inserts. However, agranulocytosis is still reported as adverse reactions. In some cases, periodic blood tests were not performed or the treatment of thiamazole was continued despite decreasing WBC/neutrophil count or related symptoms. (See Case 1 and 2 on page 2/3.)



A total of 292 cases of adverse reactions to thiamazole with documented onset time of agranulocytosis(January 2004 to November 2011), which were reported to the PMDA by November 25, 2011.

◎ Ensure periodic blood tests and advise patients to check related symptoms.

Time of onset of agranulocytosis



Since approximately 65% of patients* develop agranulocytosis within first 2 months of administration, healthcare professionals should perform periodic blood tests especially in the first 2 months of administration.
According to the Relief System for Sufferers from Adverse Drug Reactions, the relief benefits are not applicable to cases in which a drug was used improperly, for example, in cases where appropriate blood tests were not performed, leading to serious adverse reactions.

* Based on 315 cases of adverse reactions with documented onset time of agranulocytosis , which were reported to the PMDA between February 2004 and August 2011.

Thiamazole should be carefully used in patients with moderate to severe leukocytopenia or other blood disorders.

Start — 1 month — 2 months

Check differential leukocyte count once every 2 weeks.

Perform periodic blood tests.

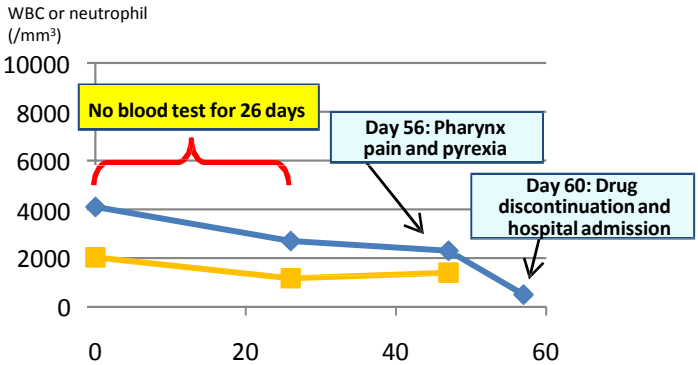
Discontinue administration of thiamazole immediately if a downward trend of differential leukocyte count is observed.

Advise patients to consult their physician immediately if any related symptoms occur.

Advise the patient to check related symptoms (pharynx pain, pyrexia, and malaise).

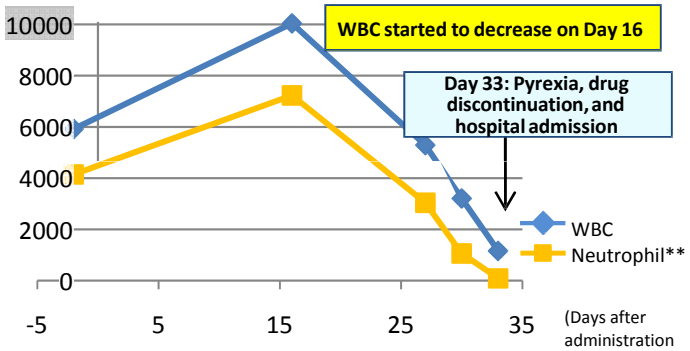
[Case Summaries]

(Case 1) A female patient in her 20s. The patient received Mercazole 30 mg/day for treatment of Basedow's disease. No blood test was performed for 26 days after administration.



	Day of administration	Day 26	Day 47	Day 57
WBC (/mm³)	4100	2700	2300	500
Neutrophil (/mm³)	2030	1175	1403	-

(Case 2) A female patient in her 50s. The patient received Mercazole 30 mg/day for treatment of hyperthyroidism. WBC was decreased on Day 30, but the administration of this drug was continued until Day 33.



	2 days before administration	Day 16	Day 27	Day 30	Day 33
WBC (/mm³)	5920	10040	5290	3210	1160
Neutrophil (/mm³)					

**Neutrophil count is calculated based on differential leukocyte count.

⚠ See "WARNINGS" and "Important Precautions" sections of package insert for blood test and symptom check.

◎ Package insert: Blood test and symptom check

[WARNINGS]

1. Serious agranulocytosis has been reported especially within the first 2 months of initial administration, leading to fatal outcomes in some cases. Blood tests including differential leukocyte counts should be performed once every 2 weeks in principle for at least first 2 months after administration, and periodically even after 2 months. If any abnormalities such as decreasing tendency of granulocyte are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken. If the administration of this drug is resumed after suspension, the same cautions should be exercised. (See the "Important Precautions" section.)

2. Prior to administration of this drug, patients should be informed of possible adverse reactions such as agranulocytosis and required blood tests. Patients should be instructed:
(1) to consult their physician immediately if any symptoms of agranulocytosis (e.g., pharynx pain and pyrexia) occur.
(2) to visit the hospital once every 2 weeks in principle for at least first 2 months of initial administration since periodical blood tests are required.

[PRECAUTIONS]

1. Careful Administration (This drug should be administered carefully in the following patients.)
(1) Patients with hepatic disorder [Hepatic disorder may be aggravated.]
(2) Patients with moderate to severe leukocytopenia or other blood disorders [Leukocytopenia or blood disorders may be aggravated.]

2. Important Precautions
(1) If administration of this drug is newly started, serious adverse reactions such as agranulocytosis may occur especially within the first 2 months of administration. This drug should be administered only to patients who are considered eligible based on the thorough review of the efficacy and safety of this drug.
(2) If the WBC is within the normal range but decreasing, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

3. Adverse Reactions
(1) Clinically significant adverse reactions
*1) Pancytopenia, aplastic anaemia, agranulocytosis, and leukopenia (incidence unknown): Pancytopenia, aplastic anaemia, agranulocytosis, or leukopenia (initial symptoms include pyrexia, general malaise, and pharynx pain) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
(See the "WARNINGS" section.)

As of December 2011

[Product name (Name of Marketing Authorization Holder)]
MERCAZOLE Tablet 5 mg, MERCAZOLE Injection 10 mg (Chugai Pharmaceutical Co., Ltd.)

See information on the precautions related to MERCAZOLE, including agranulocytosis, at the Pharmaceutical and Medical Devices Information website
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.

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