PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No. 1 August 2010

# Compliance with conduct of laboratory tests before and after administration of salazosulfapyridine

**Salazosulfapyridine (sulfasalazine) is used for the treatment of rheumatoid arthritis and ulcerative colitis. Periodic hematological, liver function, and renal function tests should be performed to prevent adverse drug reactions (ADRs) such as blood disorders and hepatic dysfunctions**

It is well known that salazosulfapyridine may cause blood disorders and hepatic dysfunctions. These ADR alerts are included in "Important Precautions" and "Clinically Significant Adverse Reactions" sections of the package insert. However, among recently reported cases, there still seems to be some cases where ADR symptoms due to salazosulfapyridine became serious because the laboratory tests were not performed at the timings described in the package insert (See "Typical Clinical Cases"). Timely laboratory tests as described in the package insert must be performed when administering salazosulfapyridine.

## " Typical Clinical Cases"

(Case 1) A female patient in her 50s with rheumatoid arthritis. WBC was 7600/mm3 before starting salazosulfapyridine (enteric tablets). Administration of salazosulfapyridine was started at 250 mg and increased to 500 mg on Day 9 of administration. On Day 36 rash accompanied by redness appeared on the upper arms, chest, and back. WBC decreased to 900/mm3 (lymphocyte 84%). Drug-induced agranulocytosis was suspected, and the patient was admitted to a sterile room. No laboratory tests were performed during treatment until the symptoms appeared.

(Case 2) A male patient in his 40s with rheumatoid arthritis. WBC was 6900/mm3 before starting administration of salazosulfapyridine (enteric tablets). On Day 43 of administration of salazosulfapyridine 1000 mg, the patient was admitted to the hospital for pyrexia and pharynx pain. WBC was 500/mm3 upon admission. The patient was diagnosed with sepsis based on a blood culture showing staphylococcus. No laboratory tests were performed during treatment until the symptoms appeared.

(Case 3) A female patient in her 50s with rheumatoid arthritis. WBC was 5380/mm3 before starting administration of salazosulfapyridine (enteric tablets). Administration of salazosulfapyridine was started at 500 mg concomitant with other drugs (loxoprofen sodium and rebamipide) and increased to 1000 mg on Day 14 of administration. Cold symptoms occurred on Day 36. On Day 38, WBC was 280/mm3. The patient was diagnosed with leukopenia and admitted to the hospital. No laboratory tests were performed during treatment until the symptoms appeared.

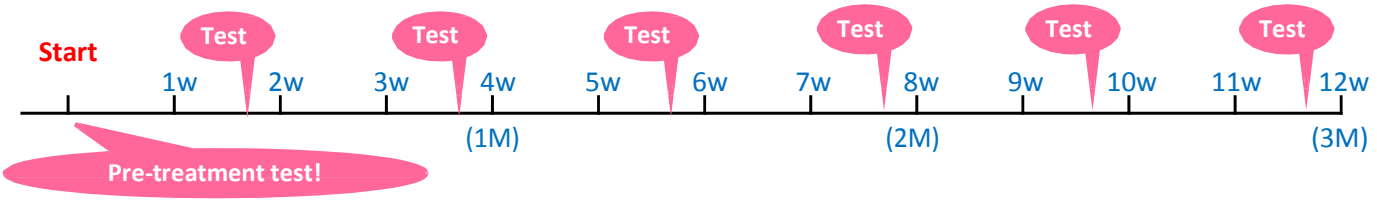
## In patients treated with salazosulfapyridine;

- ADRs may be overlooked without periodic laboratory tests. ADRs may become serious if left untreated!
- Be sure to perform periodic laboratory tests!

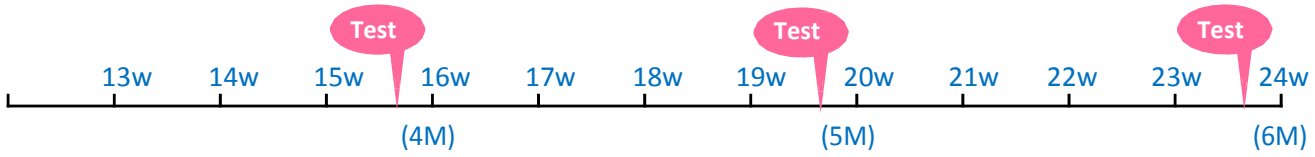
# Recommended Timing for Laboratory Tests

Hematological and liver function tests should be performed at the intervals shown below or more frequently.

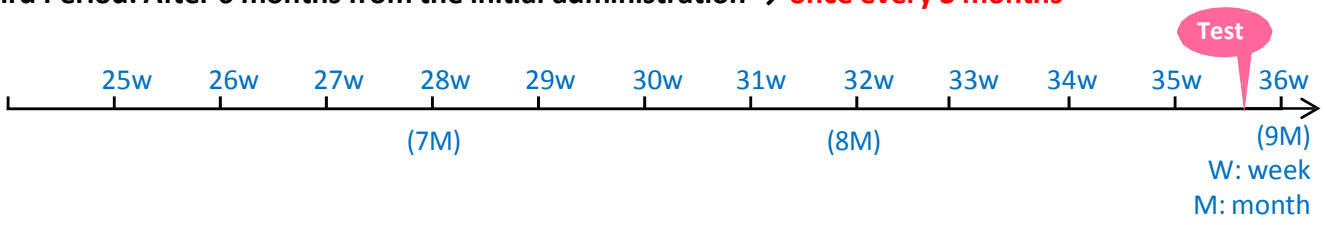
**First Period: First 3 months from the initial administration → once every 2 weeks**




**Second Period: Next 3 months → once every 4 weeks**




**Third Period: After 6 months from the initial administration → once every 3 months**




Time to onset of ADRs to salazosulfapyridine (FY2007 to FY2009)

Since ADRs occurred within 3 months of treatment in most patients, frequent tests are necessary during the first 3 months.

| Time to onset | Start to 1 month | 1 to 2 months | 2 to 3 months | After 3 months | Unknown |
|---|---|---|---|---|---|
| Blood disorder | 29 cases | 19 cases | 3 cases | 13 cases | 14 cases |
| Hepatic dysfunction | 16 cases | 4 cases | 0 case | 1 case | 2 cases |

**ADRs occurred within 3 months in most patients!**

Information about the conduct of laboratory tests are provided in “Important Precautions” section of the package insert. Read the package insert before using salazosulfapyridine.

Information about optimal timing of laboratory tests are provided in the "Important Precautions" section of the package insert of salazosulfapyridine enteric tablets, and periodic laboratory tests before and during treatment are recommended.

The package inserts for salazosulfapyridine tablets and suppository were revised in August 2010 to include the description that periodic laboratory tests should be performed at the same timing recommended for enteric tablets.

The following sentences are described in the "Clinically Significant Adverse Reactions" section of the package insert.

**"Clinically Significant Adverse Reactions"**

**Aplastic anaemia, pancytopenia, agranulocytosis, decreased platelets, anaemia (haemolytic anaemia, megaloblastic anaemia [folate deficiency], etc.), disseminated intravascular coagulation (DIC)**

Aplastic anaemia, pancytopenia, agranulocytosis, decreased platelets, anaemia (haemolytic anaemia, megaloblastic anaemia [folate deficiency], etc.) and/or disseminated intravascular coagulation (DIC) 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.

**Fulminant hepatitis, hepatitis, hepatic dysfunction, jaundice**

Hepatitis with marked elevations of AST (GOT) and ALT (GPT), hepatic dysfunction and/or jaundice may occur. It may cause hepatic failure or fulminant hepatitis. 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.

Product name of salazosulfapyridine (manufacturer)

| | |
|---|---|
| Enteric tablets: | Azulfidine EN Tablets 250 mg, 500 mg (Pfizer Japan Inc.) |
| | SOARESIN Tablet 250 mg (Taiyo Yakuhin Co., Ltd.) |
| | SAFILDINE-EN Tablet 500 (Shiono Chemical Co., Ltd.) |
| | ASASURFAN ENTERIC TABLETS 500 mg (Choseido Pharmaceutical Co., Ltd.) |
| Tablets: | Salazopyrin Tablets 500 mg (Pfizer Japan Inc.) |
| | SLAMA TAB. 500 mg (Nichi-Iko Pharmaceutical Co., Ltd.) |
| | LANOFEN Tablets (Taisho Pharm. Ind. Ltd.) |
| | SALAZOSULFAPYRIDINE Tablet 500 mg "Taiyo" (Taiyo Yakuhin Co., Ltd.) |
| Suppository: | Salazopyrin Suppositories 500 mg (Pfizer Japan Inc.) |

Information on the package insert of salazosulfapyridine is also available at the Pharmaceuticals and Medical Devices Information website (in Japanese)
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html

**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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Medical Safety
Information Group
E-mail: safety.info@pmda.go.jp
http://www.info.pmda.go.jp/