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IMPORTANT

Dear Healthcare Professionals Letter of Rapid Safety Communication BLUE LETTER

Thrombosis with YAZ[®] COMBINATION TABLETS for Dysmenorrhea

From the launch of Yaz on 16.Nov.2010 till 7.Jan.2014, 3 fatal cases with thrombosis, of which causal relationship with Yaz cannot be ruled out, have been reported (Estimated cumulative number of users: approx. 187,000 Women-Year*). Considering this situation, "WARNING" is newly added into "PRECAUTIONS" of the drug for requiring further attention.

*: Women-Year: Estimate number of users in case one woman uses 13 sheets of the drug (28 tablets in one sheet) in one year.

Please pay attention to the following points for the use of Yaz.

- Thrombosis may occur with the use of the drug and it may have a fatal outcome. If any of the following symptoms appears and thrombosis is suspected, **administration should be discontinued and appropriate measures taken immediately.**

Symptoms of which thrombosis is suspected

- Sudden severe pain/edema of the lower limb
 - Sudden breath shortness, chest pain
 - Severe headache, weakness/paralysis of extremities, dysarthria
 - Acute visual disturbance
- etc.

- Patient should be instructed to stop taking the drug and visit emergency medical institution immediately, if such symptom appears.
- Patient Card should be provided to the patient. Please instruct them to show the card when they visit the other medical institutions.

Please be informed that "WARNING" is newly added and "Important Precautions" and "Clinically significant adverse reactions" are revised.

Contact information is available in Page 3.

Revisions of Package Insert (Revision by Notice from Safety Division of Pharmaceutical and Food Safety Bureau in MHLW)

| Revised | Current |
|---|--|
| <p><u>[WARNING]</u> <u>Thrombosis may occur with the use of the drug and it may have a fatal outcome. If any of the following symptoms appears and thrombosis is suspected, administration should be discontinued and appropriate measures taken immediately.</u></p> <p><u>Symptoms of which thrombosis is suspected</u> <u>Sudden severe pain/edema of the lower limb, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc.</u></p> <p><u>Patients should be instructed to stop taking the drug and visit emergency medical institution immediately, if such symptom appears.</u> <u>[See “Contraindications”, “Important Precautions” and “Clinically significant adverse reactions”]</u></p> | <p>←New</p> |
| <p>2. Important Precautions</p> <p>(2) <u>Thrombosis may occur with the use of the drug irrespective of the existence of risk factor(s) such as age (40 years old and over), smoking, obesity, a family history of thrombosis. If any initial symptoms of which thrombosis is suspected appears, appropriate measures such as discontinuance of the drug should be taken.</u></p> <p><u>Initial symptoms of which thrombosis is suspected</u> <u>Vomiting/nausea, headache, swelling/pain/numbness of the lower limb, redness, hot feeling, etc.</u></p> <p>(3) <u>If patients are at the condition of high risk of thrombosis (immobilized condition, remarkable elevation in blood pressure, dehydration, etc.), appropriate measures such as discontinuance of the drug should be taken.</u></p> <p>(4) <u>The following explanation/instruction should be given to the patients taking this drug at the start and continuation of the use.</u></p> <ul style="list-style-type: none"> - <u>Thrombosis may have a fatal outcome.</u> - <u>Use of the drug should be stopped and consult physicians etc., immediately, if any initial symptom of which thrombosis is suspected appear and/or if at the condition of high risk of thrombosis, irrespective of the severity of the symptom/condition.</u> - <u>The use of the drug should be told to a physician at visit of other medical institution suspecting thrombosis so that the physician can consider possibility of thrombosis occurring with the use of the drug.</u> <p>(5) <u>When a surgical operation becomes necessary during the treatment with the drug, due caution should be considered to prevent thrombosis. [See “CONTRAINDICATIONS, (11)”].</u></p> | <p>2. Important Precautions</p> <p>(2) Thrombosis may occur with the use of the drug. If the following symptoms and/or conditions appear, administration should be discontinued. Patients taking this drug should in advance be instructed to consult physicians etc., immediately, if the following symptoms and/or conditions appear.</p> <ol style="list-style-type: none"> 1) Initial symptoms of thrombosis Pain/edema of the lower limb, sudden breath shortness, chest pain, severe headache, acute visual disturbance, etc. 2) High risk conditions of thrombosis Immobilized condition, remarkable elevation in blood pressure, etc. <p>(3) When a surgical operation becomes necessary during the treatment with the drug, due caution should be considered to prevent thromboembolism. [See “CONTRAINDICATIONS, (11)”].</p> |

4. Adverse Reactions

(1) **Clinically significant adverse reactions**
Thrombosis (incidence unknown): Since thrombosis (extremity, lung, myocardium, brain, retina, etc.) may occur, women should carefully be monitored. If symptoms such as sudden severe pain/edema of the lower limb, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc., occur, administration should be discontinued immediately and appropriate measures taken.

4. Adverse Reactions

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———— : Addition ===== : Deletion

- The content of revision is planned to be available on Drug Safety Information (DSU) No. 227 (Mar. 2014).

Contact Information

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