April 18, 2014 No. 14-01

IMPORTANT

Dear Healthcare Professionals Letter of Rapid Safety Communication BLUE LETTER

Fatal cases with XEPLION® Aqueous Suspension for IM injection

Since the launch of XEPLION on November 19, 2013, 21 fatal cases have been reported following XEPLION administration up to April 16, 2014 (estimated number of users is approximately 10,900 patients). The causes of death in the reported fatal cases have not been established due to insufficient information and the causal relationship between death and XEPLION use is unknown at the moment.

Considering this situation, the company have been asking for the proper use of XEPLION thorough the distribution of the "Request for Proper Use of XEPLION® Aqueous Suspension for IM injection 25mg, 50mg, 75mg, 100mg and 150mg" to show that some fatal cases were reported during use of XEPLION and to deliver details of the fatal cases. In addition, it has been decided to update the "PRECAUTIONS" in the package insert in order to further ensure the proper use of XEPLION.

Please pay attention to the following points for the use of XEPLION

- **XEPLION should not be administered in patients who are rapidly agitated, or in unstable patients that are likely to require concomitant use of many types of antipsychotics.**
  Sustained-release antipsychotics are generally used to manage relapsing psychiatric symptoms. Once XEPLION is injected, it is not possible to eliminate the drug immediately from the body. Therefore, somatic symptoms of patients should be checked and the necessity of treatment with XEPLION should be fully assessed before starting treatment with XEPLION, and due attention should be paid to the prevention and treatment of adverse reactions and overdose, etc.

- **The main active metabolite of both XEPLION and risperidone is paliperidone (9-hydroxy risperidone). Caution should be exercised in dosage and administration to avoid overdose when switching from risperidone sustained-release suspension for injection (Risperdal Consta® Intramuscular Injection) to XEPLION.**

  The following administration methods are estimated to maintain approximately as the same active metabolite levels as in steady state of Risperdal long acting injection.

Risperdal Consta	→	XEPLION
25 mg every 2 weeks	→	50 mg every 4 weeks
50 mg every 2 weeks	→	100 mg every 4 weeks

- **For patients who have never been treated with paliperidone or risperidone, stability of symptoms with oral paliperidone or oral risperidone for a certain period should be established prior to initiating treatment with XEPLION. XEPLION treatment should be started without concomitant use of oral paliperidone or oral risperidone.**
  Risperdal Consta Intramuscular Injection takes 3 weeks or more from first administration to have significant release of medication with efficacy continuing for 2 weeks. During the first three weeks, therefore, oral antipsychotics are concomitantly used. However, since XEPLION increases its plasma concentrations from first administration, concomitant use of other antipsychotics should be avoided during XEPLION treatment.

Revisions of PRECAUTIONS in the Package Insert

Revised	Current
Precaution for Dosage and Administration (2) **For patients who have never been treated with paliperidone or risperidone, response to therapy and tolerability** with oral paliperidone or oral risperidone **should be established** for a certain period prior to initiating treatment with this drug. This drug should be started without concomitant use of oral paliperidone or oral risperidone.	**2. Important Precautions** (2) **For patients who have never been treated with paliperidone or risperidone, tolerability** with oral paliperidone or oral risperidone **should be established** prior to initiating treatment with this drug.
Precaution for Dosage and Administration (6) When switching from another prolong-acting injectable antipsychotic to this drug, due attention should be paid for the timing and dosage with consideration for pharmacokinetics of drugs, and patients should be carefully monitored for their symptoms. The main active metabolite of both this drug and risperidone is paliperidone. Caution should be exercised in dosage and administration to avoid overdose when switching from risperidone sustained-release suspension for injection to this drug. The following administration methods are estimated to maintain approximately as the same active metabolite levels as in steady state of risperidon sustained-release suspension for injection. (See 'PHARMACOKINETICS') ・ Administering paliperidone sustained-release suspension for injection 50 mg at 4-week intervals after two weeks from the last dose of risperidone sustained-release suspension for injection 25 mg to a patient who was treated with **risperidone sustained-release suspension for injection 25 mg** at 2-week intervals ・ Administering paliperidone sustained-release suspension for injection 100 mg at 4-week intervals after two weeks from the last dose of risperidone sustained-release suspension for injection 50 mg to a patient who was treated with **risperidone sustained-release suspension for injection 50 mg** at 2-week intervals	**Precaution for Dosage and Administration** (5) When switching from another prolong-acting injectable antipsychotic to this drug, due attention should be paid for the timing and dosage with consideration for pharmacokinetics of drugs, and patients should be carefully monitored for their symptoms. (See 'PHARMACOKINETICS')
2. Important Precautions (1) Since sustained-release antipsychotics are generally used to manage relapsing psychiatric symptoms. This drug **should not be administered in patients who are rapidly agitated, or in unstable patients that are likely to require concomitant use of many types of antipsychotics.** Once this drug is injected, it is not possible to eliminate the drug immediately from the body. Therefore, the necessity of treatment with this drug should be fully assessed before starting treatment with this drug, and due attention should be paid to the **prevention and treatment of adverse reactions, and overdose, etc.** [See "Precautions for Dosage and Administration", "Adverse Reactions" and "Overdose."]	**2. Important Precautions** (1) Since this drug is a sustained-release preparation, **it is not possible to eliminate the drug at once from the body**. Therefore, the necessity of treatment with this drug should be fully assessed before starting treatment with this drug, and due attention should be paid to **prevention and treatment of adverse reactions, overdose, etc.** [See "Precautions for Dosage and Administration", "Adverse Reactions" and "Overdose."]

———— : revision

[Inquiry]
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