WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

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DRS Information Exchange Service

ALERT No. 38

REMOXIPRIDE (ROXIAM®) : BLOOD DYSCRASIAS REPORTED IN SWEDEN AND THE UNITED KINGDOM

The Swedish Medical Products Agency has issued the preliminary results of an investigation of reports of blood dyscrasias associated with the use of the antipsychotic dopamine antagonist, remoxipride (Roxiam®: Astra).

Remoxipride has been registered in Sweden since January 1991 for the treatment of schizophrenia and other psychoses. Known adverse effects are similar to the classical neuroleptics although sedation, extrapyramidal and anticholinergic side effects are less marked with remoxipride. Increased prolactin levels are seen after each dose but generally return to normal during the dose interval. The half-life of remoxipride is 4-7 hours but it is prolonged (about doubled) in the elderly, in patients with reduced kidney function and in those who are poor metabolizers of debrisoquine. Blood dyscrasias of various types have been reported for several neuroleptic drugs; however, clinical trials of remoxipride involving 2451 patients have given no indications that it would elicit blood dyscrasias.

The Agency was alerted by the manufacturer on 27 September that the Committee on Safety of Medicines (CSM) in the United Kingdom had received 4 reports of aplastic anaemia that developed during remoxipride treatment, one of which was fatal. All patients were women aged 35 to 43 years of age and had been treated for periods ranging from 90 to 180 days. In the UK, Astra estimated that about 12,000 patients have been exposed to remoxipride. No similar cases were reported in Sweden where about 15,000 patients have been exposed and no reports of aplastic anaemia or pancytopenia associated with remoxipride had been recorded in the data bank of the WHO International Drug Monitoring Programme. There were 7 reports of leucopenia including one of agranulocytosis, but all these were confounded by other suspected drugs.

The Medical Products Agency, in conjunction with the manufacturer, contacted doctors in Sweden in order to investigate the matter further as quickly as possible. A survey carried out in 11 major hospitals identified 26 cases of confirmed and 5 of suspected aplastic anaemia but no information was available about exposure to remoxipride.

Two cases were identified among spontaneous reports:

1. A 35-year old male patient who had received remoxipride 150 mg twice daily for several months for schizophrenia who developed thrombocytopenia with fatal outcome.

2. A 54-year old female patient who was hospitalized with leucopenia and thrombocytopenia. A bone marrow biopsy confirmed aplastic anaemia. She had been treated with remoxipride 300 mg twice daily as well as clomipramine 75 mg per day, diclofenac 50 mg per day and propiomazine 50 mg at night.

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Several other cases identified in the survey need to be followed up to ascertain whether remoxipride is implicated. In the meantime, the Medical Products Agency wishes to draw attention to the probable causal relationship between remoxipride and serious blood dyscrasias.[1]

After receiving the data on the 4 cases of aplastic anaemia reported to the Committee on Safety of Medicines and after a joint meeting on 1 October, the manufacturer agreed to amend the data sheet for remoxipride to include the following statements:

"Roxiam® should not be used in patients with a history of haematological malignancy or blood dyscrasias, such as leucopenia, thrombocytopenia or severe anaemia. Particular care should be taken with patients previously exposed to drugs known to cause these reactions.

"When starting treatment with Roxiam® a full blood count should be requested and patients should only continue therapy if this is normal. Patients should be instructed to promptly report the development of bruising, bleeding, fever, sore throats or other signs of infection whilst on treatment. If an abnormal blood count is found, Roxiam® should be stopped immediately and the patient referred for specialist haematological evaluation."

The manufacturer has also sent a letter to doctors informing them of these changes and requesting them to report any cases of suspected aplastic anaemia that they may encounter.[2]

The Committee on Safety of Medicines issued a pharmacovigilance alert to Member States of the European Communities on 6 October 1993 informing them of the 4 reports of aplastic anaemia in patients receiving remoxipride and requesting them to report any relevant information.[3]

References:

1) Communication form the Medical Products Agency, Uppsala, Sweden, dated 19 October 1993.
2) "Dear Doctor" letter from Astra dated 11 October 1993.
3) Medicines Control Agency Pharmacovigilance Rapid Alert dated 6 October 1993.

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