European Medicines Agency

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QUESTIONS AND ANSWERS ON NEUPRO (rotigotine)

The European Medicines Agency (EMEA) has been made aware by Schwarz Pharma Ltd of a problem of crystals forming within the patches of Neupro, a medicine used for the treatment of Parkinson's disease.
As this problem can be managed by storing the medicine in the refrigerator, the EMEA's Committee for Medicinal Products for Human Use (CHMP) has agreed that the company should immediately change its advice on Neupro's storage conditions. In addition, all existing stocks of the medicine are being gradually removed from the European Union markets and are being replaced by new stock.

What is Neupro?

Neupro is used either on its own or with other medicines to treat patients with Parkinson's disease. It is used on its own only in the early stages of the disease. It is available as transdermal patches (patches that deliver the medicine across the skin) releasing 2, 4, 6 or 8 mg rotigotine over 24 hours. Neupro was first authorised in the European Union (EU) in February 2006, and is currently available in Austria, the Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Norway, Poland, Spain, Slovakia, Sweden and the United Kingdom.

The active substance in Neupro, rotigotine, is a dopamine agonist: it imitates the action of dopamine. Dopamine is a messenger substance in the parts of the brain that control movement and coordination. In patients with Parkinson's disease, the cells that produce dopamine begin to die and the amount of dopamine in the brain decreases. The patients then lose their ability to control their movements reliably. Neupro delivers a constant supply of rotigotine through the skin into the bloodstream. Rotigotine stimulates the brain as dopamine would, so that patients can control their movement and have fewer of the signs and symptoms of Parkinson's disease, such as stiffness and slowness of movement.

What is the problem with Neupro?

The company that makes Neupro, Schwarz Pharma Ltd has noticed that there is crystal formation (crystallisation) within some of the Neupro patches. This occurs when the rotigotine in the patch turns into solid crystals that resemble a snowflake. These 'snowflakes' are visible within the patch, and in some batches, the crystallisation can be seen on up to 40% of the surface of the patch.

What were the concerns of the CHMP?

The CHMP had concerns regarding the effectiveness of the medicine: when rotigotine is in this crystal form, it is less soluble. This could affect its release from the patch into the bloodstream and may make patches less effective.

However, the CHMP also acknowledged that patients who are using Neupro can have an advanced form of Parkinson's disease; they may be receiving many medicines and their quality of life may be poor. If Neupro were to become suddenly unavailable, these patients would need to switch their treatment to another dopamine agonist. Switching from the patches to another medicine takes time and might mean additional visits to the doctor. It could also lead to problems with over- or under-treatment while dosages are adjusted.

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What were the conclusions of the CHMP?
Looking at the data presented by the company, the CHMP concluded that there was evidence that keeping Neupro patches below 5°C reduces the growth of crystals. The Committee recommended that the company immediately changes its recommendation regarding the way the medicine is stored. This will help to ensure that patients can continue using their Neupro.

The CHMP also looked at the measures the company is putting in place to ensure that crystal formation is controlled in newly made stocks. In order to avoid a shortage of Neupro, the Committee has recommended that all packs of Neupro that have already been sent to wholesalers and pharmacies are replaced at the same time with stocks that have been made and handled in such a way that crystal formation is less likely. This will ensure that the supply of Neupro continues while the company puts extra measures in place in its factories.
This replacement will start using stock the company already has, that has been kept in cold storage. This existing stock will be overlabelled with a sticker indicating the new storage conditions so that pharmacists and patients are aware of the change. The company is working on making new stock under a 'cold chain' system (when all locations where the patches are made, stored and distributed are kept at the appropriate temperature). Once this stock is available, it will be used in the replacement exercise.
In all cases the patches will also be given a shorter shelf life.

To ensure that the replacement process can be carried out successfully across the EU, the company will use a phased approach. The replacement will start at a different date in each country. In the end, all stocks will have been replaced within three months.

What are the consequences for patients?
- Patients who are currently receiving Neupro should not stop their treatment suddenly.
- Patients should store the patches they have at home in the refrigerator.
- While the company is working on the replacement operation, patients will only be able to get a prescription for one month's supply at a time.
- Patients who have concerns should contact their doctors or pharmacists. They also should do so if they notice snowflakes patterns within their patches.

What are the consequences for doctors?
- Doctors should not prescribe Neupro to any new patients until further notice.
- Doctors should only prescribe Neupro for one month at a time. The larger pack sizes of Neupro will not be available. There may also be some temporary shortages of the 6 and 8 mg/24 hours patches.

What are the consequences for pharmacists?
- Pharmacists need to store their existing stocks of Neupro in the refrigerator.
- When the replacement process starts, pharmacists will be contacted by the company regarding the replacement of their existing stock. The replacement stock will be labelled with the new storage conditions and shelf life.

What will happen next?
The company that makes Neupro is building its 'cold chain' within the organisation to make sure that Neupro patches are handled at the appropriate temperature from the factory to the patient. This should be in place within the next three months. The company is also looking at measures that may help prevent the formation of crystals, and could consider changing the way the medicine is made.

The company has also committed not to launch Neupro in the EU countries where it is not yet available. It has also committed not to launch Neupro in the new indication of the treatment of restless legs syndrome for which the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in April 2008.

The EMEA will update this document as new information becomes available.