

AUG 2014

Re: FENTANY JANSSEN: Introduction of New Warning - Serotonin syndrome may occur under co-administration with serotonergic drugs

Dear Healthcare provider,

J-C Health Care Ltd. would like to inform you of the following:

Summary

This communication is being distributed to alert you to the possibility of serotonin syndrome when serotonergic drugs are administered concomitantly with the Company's fentanyl-containing products, including FENTANY JANSSEN. Serotonin syndrome is a potentially life threatening condition.

If serotonin syndrome is suspected, rapid discontinuation of FENTANY JANSSEN should be considered.

The information is being sent in agreement with the Israeli MOH.

Further information on the safety concern and the recommendations

The Company undertook a review to assess the available evidence for the possibility of serotonin syndrome when serotonergic drugs are administered concomitantly with fentanyl-containing products that are currently licensed by the Company. Based on the results and conclusions of this review, updates to the Summary of Product Characteristics for FENTANY JANSSEN have been made to include a warning regarding the potential for serotonin syndrome to occur when FENTANY JANSSEN is used concurrently with other serotonergic drugs.

- Caution is advised when FENTANY JANSSEN is co-administered with drugs that affect the serotonergic neurotransmitter systems.
- The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of
 - serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs)
 - Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs)
 - Drugs which impair the metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs])
- This may occur within the recommended dose.

Serotonin syndrome may include one or more of the following:

- mental-status changes (e.g., agitation, hallucinations, coma)
- autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia)
- neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity)
- gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea)

If serotonin syndrome is suspected, rapid discontinuation of FENTANY JANSSEN should be considered.

Further information

Serotonin syndrome is often described as a clinical trial of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities as a consequence of excess serotonergic agonism of central nervous system receptors and peripheral serotonergic receptors. Symptoms can develop rapidly, often within minutes of drug exposure. Approximately 60% of patients with serotonin syndrome present within 6 hours after initial use of medication, an overdose, or a change in dosing.

(Reference: Boyer EW, Shannon M. The Serotonin Syndrome, N Engl J Med. 2005; 352: 1112-1120)

Cases of serotonin syndrome have been reported with the use of FENTANY JANSSEN when given concomitantly with other drugs known to be associated with serotonin syndrome. The role of fentanyl in the development of serotonin syndrome in these cases is unclear because there is a lack of pharmacological evidence for biological plausibility. Some animal studies have suggested that fentanyl may have serotonergic properties.

Serotonin syndrome is not an adverse drug reaction (ADR) associated with the use of FENTANY JANSSEN when it is administered alone. The cases of serotonin syndrome that have been reported occurred when serotonergic drugs were administered concomitantly with a fentanyl-containing product.

Call for reporting

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Israeli Ministry of Health on

[http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectM
edic@moh.heal th.gov.il](http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.heal th.gov.il) or ADR@moh.health.gov.il

Additionally it should be reported to the following:

e-mail: tcohen@its.jnj.com

TL: 0544-307281

Yours faithfully,

**Liliana Balter,
RA Manger
J-C Health care , Ltd.**