



**JANSSEN**  
SIN EL-FIL  
GENERAL CHEHAB AVENUE  
(Near Clinique du Levant)  
Beirut-LEBANON

Malta

July 9<sup>th</sup>, 2013

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

Dear Healthcare provider,  
Janssen-Cilag International NV 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 SUBLIMAZE. Serotonin syndrome is a potentially life threatening condition.

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

The information is being sent in agreement with the Medicines Authority

***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 SUBLIMAZE have been made to include a warning regarding the potential for serotonin syndrome to occur when SUBLIMAZE is used concurrently with other serotonergic drugs.

- Caution is advised when SUBLIMAZE 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 SUBLIMAZE should be considered.

#### ***Further information***

Serotonin syndrome is often described as a clinical triad 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 SUBLIMAZE 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 SUBLIMAZE 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***

**Any suspected adverse drug reactions can be reported to:**

Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: <http://www.medicinesauthority.gov.mt/pub/adr.doc>

Or to

**AM Mangion Ltd, N/S off Valletta Road, Luqa LQA 6000, Telephone Number + 356 2397 6333 or on [pv@ammangion.com.mt](mailto:pv@ammangion.com.mt)**

**Communication information**

Should you have any questions please contact:

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The responsible contact persons in Malta  
Miss. Maria Cuschieri, Senior Regulatory Affairs Associate  
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Yours faithfully,

**Hassan Bibi**

**Regional Regulatory Affairs Director**  
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Fentanyl citrate Jan 2013

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