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

Malta
March 14, 2013

Healthcare Professional Communication (DHPC)

Re: Durogesic: Introduction of New Warning - Serontonin 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 Durogesic. Serotonin syndrome is a potentially life threatening condition.
If serotonin syndrome is suspected, treatment with Durogesic should be discontinued.

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

- Caution is advised when Durogesic 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, treatment with Durogesic should be discontinued.

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 Durogesic 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 Durogesic 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/adrportal
Alternatively, adverse events may be reported to the address representing the Marketing Authorisation Holder under **Communication information** below:

Communication information

If you have any questions please don't hesitate to contact.

Janssen Regional Office:

Mr. Hassan Bibi, Regional Regulatory Affairs Director
Dr. Tony Bou Khalil, Medical Affairs Manager
Tel: (+961.1)518700
Fax: (+961.1)518793

Or

The responsible contact persons in Malta
Mr. Alan Mulligan, Regulatory Affairs Coordinator
Tel: + 356 2397 6000

Marketing Authorisation Holder:
Janssen-Cilag International, Turnhoutseweg 30, 2340 Beerse, Belgium.

Yours faithfully,

Fady Khayat	**Hassan Bibi**	**Tony Bou Khalil M.D.**
Area General Manager **Janssen** **NEWAAT**	**Regional Regulatory Affairs Director** **Janssen** **NEWAAT**	**Medical Affairs Manager** **Janssen** **NEWAAT**