24th June 2013

Re: Durogesic DTrans Transdermal Patch (fentanyl): Introduction of New Warning - Serotonin syndrome may occur under co-administration with serotonergic drugs

Dear Healthcare Provider,

Janssen 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 DTrans Transdermal Patch. Serotonin syndrome is a potentially life threatening condition.

If serotonin syndrome is suspected, rapid discontinuation of the Durogesic DTrans Transdermal Patch should be considered.

The information is being sent in agreement with the Irish Medicines Board.

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 DTrans Transdermal Patch have been made to include a warning regarding the potential for serotonin syndrome to

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occur when Durogesic DTrans Transdermal Patch is used concurrently with other serotonergic drugs.

- Caution is advised when Durogesic DTrans Transdermal Patch 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 Durogesic DTrans Transdermal Patch 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 Durogesic DTrans Transdermal Patch, 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 DTrans Transdermal Patch 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.

The revised Durogesic DTrans Transdermal Patch Summary of Product Characteristics (SmPC) and Patient Information Leaflet can be found electronically on medicines information online, via the website at www.medicines.ie

Call for reporting

Suspected adverse reactions associated with the use of Durogesic DTrans Transdermal Patches should be reported to the Irish Medicines Board, using a Yellow Card obtained either from the IMB, or electronically via the website at www.imb.ie. Adverse reactions can also be reported to the IMB by calling on (01) 676 4971.

Suspected adverse reactions should also be reported to Janssen-Cilag on tel: +44(0)1494 567447, fax: +44(0)1494 567799 or by e-mail at dsafety@its.jnj.com .

Company contact point

If you have further questions, including requests for a printed copy of the Summary of Products Characteristics, please do not hesitate to contact the Janssen Medical Information department on 1800 709122.

Yours faithfully,

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Head of Medical Affairs.
Janssen Ireland