STDG. 71581.P

NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EC to the PRAC made by Italy – AIFA:

Active substances	Zolpidem All pharmaceutical forms All dosages ATC Code: N05CF02
Marketing Authorisation Holders in the referring Member State	Sanofi-Aventis Recherche & Dèveloppement (originator) All other MAHs

[redacted]

Zolpidem is a hypnotic agent with the indication of short-term treatment of insomnia in the situations where insomnia is debilitating or is causing severe distress for the patient.
Zolpidem belongs to the imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents. Zolpidem preferentially binds the omega-1 receptor subtype (benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes.
The first marketing authorization (MA) was received in France (national procedure) in 1987, and zolpidem is currently approved and marketed in about 80 countries. In the European Union (EU) countries, the available pharmaceutical forms of zolpidem are 5 mg and 10 mg film-coated tablets, immediate-release (IR) formulation. Outside of the EU countries, extended-release (CR) formulations of 6.25 and 12.5 mg are available.

In January 2013 the FDA issued a Drug Safety Communication on zolpidem, requiring the manufacturers of zolpidem-containing medicines to lower the recommended dose, after new data showed that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving.

As a consequence the Marketing Authorization Holder (MAH), following FDA request, modified the prescribing information in the USA. In particular, the recommended dose was reduced to 5 mg for women and either 5 or 10 mg for men. A recommendation for zolpidem to be taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening was included. It was also given the possibility to increase the dose to 10 mg if the 5 mg dose is not effective. The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

Following the FDA communication, Italy performed a search in EudraVigilance (EV) of cases associated with zolpidem and impaired driving ability as well as road traffic accidents, the results of which were discussed at the PRAC plenary in February 2013.

Considering the FDA communication and in light of the cases from EV, the PRAC issued a recommendation requesting the MAH of Stilnox (innovator product for zolpidem) to submit a cumulative review of spontaneous cases, clinical studies and published literature of 'Impaired driving ability', 'Road traffic accident' and 'Somnambulism' associated with zolpidem. The request specified that all data should be analysed by posology (especially in the elderly), liver impairment (none, mild, moderate, severe) and time-to-onset since last dose, as available. In addition the MAH was requested to provide an overview of pharmacokinetics data, taking into consideration possible sex differences.

Data from cumulative review showed:

i) high number of spontaneous reports relative to "Impaired driving ability"(n=924; serious n=795), "road traffic accident"(n=688) and "Somnambulism"(n=3322) including "sleep driving" (n=248; 7.5% of total somnambulism);

ii) the posology, when available ("Impaired driving ability" n=209; "Somnambulism" n=733), was mainly ("Impaired driving ability" n=173; 83%; "Somnambulism" n=657; 90%) within the recommended dose for CR formulation in adults (≤6.5-12.5 mg),

iii) possible zolpidem PK influencing factors (liver impairment, elderly patients) were under represented (2.2% liver impairment, 7% elderly).

In light of the data provided in the cumulative review performed by the MAH and taking into consideration of the recent FDA approved label changes specifying new dosing recommendations for zolpidem products, the PRAC in its June 2013 meeting has issued the following recommendation:

- The PRAC considers that no changes to the zolpidem product information are necessary at this time.

- The PRAC noted that Italy is considering the need for a full review to optimize the benefit-risk of zolpidem in the authorised indication(s) and for the recommended dosage in the interest of the European Union.

Having considered data from the above mentioned cumulative review, lower doses of zolpidem could reduce the probability for next-morning impaired mental alertness including impaired driving ability. Moreover a dose reduction could also reduce the risk of somnambulism. However, given the uncertainty regarding the impact of a reduced dose on the efficacy, there is a need to obtain additional efficacy and safety information and to conduct further analyses of cumulative data, before any final position is reached.

AIFA considers that it is in the interest of the Community to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.

[redacted]

Date
04.07.13

[redacted]