NOTIFICATION TO THE PRAC 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 France - ANSM

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	Oral bromocriptin-containing products authorised for inhibition of lactation (Parlodel® and generics)
Applicant(s)/Marketing Authorisation Holder(s) - In the referring Member State	MEDA PHARMA SANOFI AVENTIS France

Bromocriptin is authorised across Europe in the indication "inhibition of lactation".

In the mid 1990s, further to the reporting of cardiovascular adverse events in women treated with bromocriptin-containing products for lactation inhibition, the FDA and the Canadian authorities withdrew this indication in 1995 and in 1994, respectively.
Concomitantly, following a first pharmacovigilance survey, the SmPC had been reinforced in France, particularly with respect to the cardiovascular ADRs (sections 4.3, 4.4, 4.5 and 4.8).

However, serious cases of cardiovascular ADRs (in particular myocardial infarction, stroke and severe hypertension) continued to be reported. This led the French authority to conduct a second pharmacovigilance survey focusing on ADR reported with bromocriptin used in lactation inhibition.
This second survey was recently finalised and confirmed an increase in the reporting rate of serious cardiovascular ADRs compared with the previous one (5.1 vs. 3.36 cases/ 100 000 patients treated), despite the reinforcement of the SmPC in 1994. Moreover, in about 60 % of the cases, the use of bromocriptin did not comply with the SmPC (e.g. non-respect of the contraindications, prescription in women with cardiovascular or neuropsychiatric risk factors, non-respect of the dosage, failure to quickly discontinue treatment upon the first signs of ADR).
Based on these pharmacovigilance data, a re-evaluation of the benefit/risk ratio of oral bromocriptin-containing products in lactation inhibition was undertaken by France in April 2013.

Analysis of safety data based on the French pharmacovigilance database and on the global safety data provided by the MAHs on the period between 1985 and 2012, revealed very rare, but potentially serious/fatal ADRs that carry a risk of sequelae, in particular cardiovascular events (myocardial infarction, ischaemic stroke, other ischaemic ADRs), neurological ADRs (convulsions) and psychiatric ADRs (hallucinations, manic episodes) occurring after the use of bromocriptin-containing products for lactation inhibition. Four deaths were reported on the global safety data. Three of them had a cardiovascular origin: stroke, myocardial infarction and carotid artery thrombosis

Thus, taking into account that the risk minimisation measures taken in France in 1994 with the reinforcement of the French SPC were insufficient to limit ADRs and misuse, the safety concerns identified with bromocriptin-containing products are considered unacceptable, especially in view of the target indication (*prevention or suppression of physiological lactation*) which is not a disease but a physiological mechanism that ceases spontaneously once the infant is not breastfed for a week or two.

There are other medicinal products authorised in this indication when medicinal lactation suppression is desired: in France, lisuride and cabergoline. Although both of these medicinal products are also dopamine agonists, pharmacovigilance data and literature pertaining to them do not reveal cardiovascular or neuropsychiatric serious adverse events with use after birth or a termination of pregnancy.

In light of the above, and given the widespread use of bromocriptin in lactation inhibition, ANSM considers that it is in the interest of the Union to refer the bromocriptin-containing products used for the *prevention or suppression of physiological lactation in the immediate post-partum period and in the late post-partum period* to the PRAC and requests that it gives a recommendation under Article 31 of Directive 2001/83/EC, as amended, on whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.

Lastly, the benefit-risk ratio of bromocriptin-containing products in the other approved indications in France (i.e. treatment of Parkinson's disease and hyperprolactinemia) are not falling in the scope of this referral.

Signed:

Date: 17 JUIL. 2013