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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## Assessment report

Procedure under Article 31 of Directive 2001/83/EC resulting from  
pharmacovigilance data

Bromocriptine-containing medicinal products for oral use indicated in post-  
partum inhibition of lactation

International non-proprietary name: bromocriptine

Procedure number: EMEA/H/A-31/1379

### Note

Assessment report as adopted by the PRAC and considered by the CMDh with  
all information of a commercially confidential nature deleted.



# Table of contents

<b>1. Background information on the procedure .....</b>	<b>3</b>
<b>2. Scientific discussion .....</b>	<b>3</b>
2.1. Introduction.....	3
2.2. Clinical safety .....	4
2.2.1. Clinical studies .....	4
2.2.2. Post marketing experience.....	5
2.2.3. Published literature .....	7
2.2.4. Other pharmacovigilance activities.....	9
2.2.5. Overall discussion on safety .....	9
2.3. Pharmacodynamic .....	11
2.4. Clinical efficacy .....	11
2.4.1. Clinical studies .....	11
2.4.2. Literature data .....	13
2.4.3. Overall discussion on efficacy.....	14
2.5. Overall benefit-risk assessment.....	14
2.6. Changes to the product information.....	15
<b>3. Overall conclusion and grounds for the recommendation .....</b>	<b>16</b>
<b>Appendix 1 .....</b>	<b>17</b>
<b><i>Divergent positions</i>.....</b>	<b>17</b>

## 1. Background information on the procedure

Bromocriptine is used to prevent or suppress lactation in women who have given birth. Within the European Union (EU) it is also used to treat other conditions such as hyperprolactinaemia and Parkinson's disease; however these indications are not in the scope of this European review.

A review of the benefit-risk balance of bromocriptine for the indication post-partum inhibition of lactation was requested on 17 July 2013 by the French competent authority (ANSM) pursuant to Article 31 of Directive 2001/83/EC, following concerns in France over rare but potentially serious or fatal side effects, particularly cardiovascular side effects (such as heart attack and stroke), neurological side effects (such as fits) and psychiatric side effects (such as hallucinations and manic episodes). The ANSM considered that the risk of these events is not acceptable in view of the fact that lactation is a natural process that eventually stops if the infant is not breastfed and referred the matter to the PRAC.

## 2. Scientific discussion

### 2.1. Introduction

Bromocriptine is used to prevent or suppress lactation in women who have given birth. In the EU it is also used to treat other conditions in the EU, such as hyperprolactinaemia and Parkinson's disease; however these indications are outside the scope of this referral and will not be discussed further. Women may not always breastfeed after childbirth due to different reasons ranging from stillbirth and HIV-infection of the mother to personal choice. Although milk production eventually stops, women in the meantime might experience breast engorgement, leakage of milk, discomfort and pain.

Bromocriptine, an ergoline derivative, is a dopamine receptor agonist; through this pathway it inhibits the secretion of prolactin a hormone which stimulates the mammary glands. As a result, bromocriptine prevents or suppresses milk production.

Bromocriptine containing medicinal products for oral use, including generics, have been authorised nationally and are available on prescription as tablets and capsules in Norway and all EU member states except Italy, Latvia and Malta.

In the mid-1990s the indication of lactation was withdrawn in the United States and some other countries in view of reports of cardiovascular adverse events (AEs) in women treated with bromocriptine-containing products for lactation inhibition. Concomitantly, in France, following a first national pharmacovigilance survey that showed that cardiovascular adverse drug reactions (ADRs) accounted for an important proportion of the AEs reported, the summary of product characteristics (SmPC) had been reinforced with respect to these ADRs.

A second French national pharmacovigilance survey, finalised in 2012, showed 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, bromocriptine was not used in line 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).

Thus, considering that the risk minimisation measures taken in 1994 with the reinforcement of the French national SmPC were insufficient to limit ADRs and misuse in France, and taking into account that the target indication (prevention or suppression of physiological lactation) is not a disease but a

physiological mechanism that ceases in one to two weeks if the infant is not breastfed, the ANSM concluded that the safety concerns identified with bromocriptine-containing products were unacceptable.

In light of the above, and given the widespread use of bromocriptine in lactation inhibition, the ANSM considered that the benefit/risk ratio of bromocriptine-containing products in this indication is unfavourable and that it is in the interest of the Union to refer the bromocriptine-containing medicinal products for oral use indicated in post-partum inhibition of lactation to the PRAC and requested in July 2013 that it gives a recommendation under Article 31 of Directive 2001/83/EC, on whether marketing authorisations of these products should be maintained, varied, suspended or withdrawn.

## **2.2. Clinical safety**

In its assessment the PRAC considered the data from clinical trials, post-marketing experience, and pharmacoepidemiological studies submitted by the MAHs as well as published literature and data available to the Member States.

### **2.2.1. Clinical studies**

The initial development plans for bromocriptine in lactation inhibition comprised 38 clinical trials in a total of 1203 women of which 946 received bromocriptine, 196 another ablacting agent and 61 placebo. In the dose-finding trials in which 423 women were treated with doses of bromocriptine ranging from 2.5 mg to 7.5 mg per day for 10 to 14 days. In the comparative trials and the open trials 198 and 323 women, respectively, were treated with 5 mg of bromocriptine per day for 14 days.

All cardiovascular variables (pulse, electrocardiography (ECG), haemodynamics) were observed within normal range. No pathological changes were found in the blood picture, liver function, urinalysis and blood clotting time. The following side effects were reported among the women treated with bromocriptine: nausea 27 (2.8%), dizziness 20(2.1%), headache 17 (2.0%), vomiting 7 (0.7%), nasal congestion 6 (0.6%), sickness 5 (0.5%), burning sensation of the breast 3 (0.3%), nervousness 1 (0.1%) and others (0.1%). No details were recorded for the events "burning sensation of the breast", however, retrospectively it is not considered as a symptom of acute myocardial infraction.

In a short-term tolerance study, 132 female volunteers (84 received bromocriptine, 48 placebo) received single doses of up to 3 mg and daily doses of up to 15 mg (divided into 3 doses of 5 mg) were for 4 to 7 days. Overall treatment was well tolerated, side effects were not markedly different from those recorded with placebo. No clinically relevant changes were found in blood parameters. ECG was recorded in 83 individuals and did not reveal any pathological effects of the drug when administered either once (2.5 and 5 mg), in increasing doses from 3 to 15 mg daily for a total of 7 days or in doses of 2.5 mg twice daily for 2 weeks. No haemodynamic changes were observed after single dose administration.

In a long term tolerance study, no relevant changes in blood pressure, nor changes in clinical chemistry were observed after up to six months of treatment.

The results of other supportive clinical studies were also presented. In a study testing the effect of bromocriptine on painful breast engorgement accompanying milk let-down and incipient mastitis in a total of 98 women were treated with bromocriptine (Del Pozo, 1978 [1]). Side effects were minimal (dizziness, nausea) and corresponded to the already known adverse reactions of bromocriptine. Laboratory tests were not performed because therapy partly consisted of only one single dose. No

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<sup>1</sup> Del Pozo E. In painful breast engorgement of milk letdown and incipient puerperal mastitis. Sandoz, 19th June 1978

relevant side effects were observed in another study in the treatment of post-partum mastitis (Peters, 1977 [2]).

An open study in 36 women given 2.5 mg once or twice daily to treat painful breast engorgement in the post-partum and several other studies focussed on clinical signs of ab lactation and suppression of prolactin levels. No side effects were attributed to the treatment.

In a hospital study, 2.5 mg twice daily of bromocriptine were administered to 50 women for 14 days. Bromocriptine was generally well tolerated. In only one case medication had to be discontinued after a week due to an allergy-type rash.

### 2.2.2. Post marketing experience

A search in the safety database of the MAH of the originator between 1973 and 09 February 2014 retrieved 1,479 cases worldwide including 382 from the EU related to the indication inhibition of lactation. With regards to the safety concerns associated with cardiovascular, neurological and psychiatric disorders, the AEs from the four system organ classes (SOCs) "cardiac disorders", "nervous system disorders", "psychiatric disorders", and "vascular disorders" were evaluated and are presented in the below table. The patient exposure could not be computed accurately in the indication of interest but was estimated between about 900,000 and 7,250,000 in the EU, this yield to overall incidence rates of about 0.005% to 0.04% over the past 40 years (1973-2014).

**Table 1.** Adverse events recorded in the safety database of the MAH of the originator, reported worldwide between 1973 and February 2014 in the SOC cardiac disorder, nervous disorder, psychiatric disorder and vascular disorder.

SOCs	Seriousness		Causality assessment			Medically confirmed		Source			Total events
	Non-serious	serious	Non-assessable	Not suspect	Suspect	No	Yes	Literature	Post-marketing studies	Spontaneous reports	
Cardiac disorders	42	218	156	35	69	110	150	63	0	197	260
Nervous system disorders	558	1,102	1,108	234	318	763	897	169	1	1,490	1,660
Psychiatric disorders	121	260	235	34	112	150	231	126	0	255	381
Vascular disorders	160	290	285	52	113	201	249	69	2	379	450
Total events	881	1,870	1,784	355	612	1,224	1,527	427	3	2,321	2,751

<sup>2</sup> Peters F, Breckwoldt M. Neue Aspekte bei der Behandlung der puerperalen Mastitis. Dtsch med Wschr. (1977); 102: 1754-8.

## Fatal cases

Fifty-nine cases (4% of the total number of cases) were retrieved from a search in the safety database of the MAH originator; none occurred after 2007. Of the 59 deaths, 14 were due to cardiovascular events, 26 to neurovascular events, 1 to a psychiatric event and in 18 cases no enough information was provided (of note, among the 18 cases, one case of pneumonia and one foetal death were reported).

In twenty-four of these 59 cases causality to bromocriptine was suspected. In 16 of these 24 cases with suspected causality, patients were at increased risk, while in two cases a discrepant dose and therapy duration was observed. Overall, only 6 of these 24 cases were identified with no contraindications, discrepant dosing/therapy duration and no additional risk factors reported.

### *Cardiovascular fatal cases*

In four of the 14 fatal cardiovascular cases, the patients who were administered 2.5 mg twice a day had predisposing risk factors. One heavy smoker patient with history of arteriosclerosis of the coronary artery died of acute myocardial infarction due to a right coronary artery thrombosis. A patient hospitalised during her pregnancy due to hypertension and marked proteinuria, complained of blurred double vision, later developed seizures and became unconscious before dying due to cardiac arrhythmia. A woman with history of hypertension in pregnancy and congestive cardiomyopathy developed manifestations of pre-eclampsia during labour, and died around a week later of congestive heart failure secondary to cardiac dysrhythmia potentiated by electrolyte imbalance after having experienced nausea and vomiting. A heavy smoker with precedent of cardio-respiratory arrest, suddenly experienced intense cervicalgia followed by posterior cephalalgia, thoracic pain and loss of consciousness. The patient died 7 days later of post-partum cardiocirculatory arrest with an initial recuperation of cardiac activity and with a final outcome of multivisceral failure leading to death.

Limited information was available in eight cases but risk factors were reported: pre-eclampsia during or after pregnancy in two cases, severe hypertension and headache followed by seizures in one case, cardiomyopathy and chronic hypertension in one case, in another case, severe headaches, nausea, vomiting and dizziness preceded the death and in one case the patient had congenital prolonged QT syndrome.

In two cases no predisposing factors were identified, although mild hypertension was observed and patients experienced nausea, prolonged vomiting and headache or headache, general malaise. Death was attributed to cardiac arrest attributed to hypertensive crisis, hypokalaemia and ventricular fibrillation leading to irreversible hypoxic brain damage, and to hypertensive cardiomyopathy with evidence of focal interstitial myocardial inflammation and occurred.

### *Neurological fatal cases*

In six cases predisposing factors were observed. One heavy smoker with a family history early cerebrovascular accident complained of intense headaches, suffered a left hemiplegia the following day, which progressed to coma until she was pronounced brain dead. One case concerned an obese smoker hospitalized 20 days post-partum further to headache, paresthesia in the left hand, vomiting and stiff neck. These symptoms developed rapidly into left hemiplegia, right facial paralysis and obtundation, the patient died four days later. Bromocriptine was reported as possibly associated with the vasospasm. One smoker with history of diabetes mellitus developed a headache followed by uncontrollable hypertension and died the next day from a pulmonary embolism. One patient with history of headaches after childbirth complained of an increasing frequency of her headaches as well as

of tinnitus and blurred vision during epidural anaesthesia for a post-delivery tubal ligation. She was noted to have an episode of projectile vomiting followed by sinus bradycardia that led to cerebral death. One patient with history of preeclampsia experienced nausea, vomiting and headaches, followed by seizure, a CT scan revealed generalized cerebral oedema. The patient subsequently became unresponsive with no cerebral or brain stem function and died on post-partum day 3. A patient with elevated blood pressure died of cardiac arrhythmia after suffering headaches, vomiting, seizures, a cardiac arrhythmia, respiratory and cardiac arrest eight days after initiating therapy with bromocriptine.

In four cases however no predisposing factors were identified. Two women died of acute coronary artery thrombosis after having experienced acute seizures and chest pain. One patient developed cerebral oedema and brain death after having experienced headache, fainting and severe hypertension. One woman complained of frontal headache and bronchitic symptoms, was diagnosed with pneumonia, lost consciousness 4 days later, went on respiratory arrest and brain death.

In 16 cases limited information was available: one patient died two years after treatment cessation of a possible stroke, one patient who suffered of puerperal psychosis died of pulmonary embolism, in one case mild eclampsia was reported prior to intracerebral haemorrhage and in one case convulsion and hypertension were reported before death from cerebral ischaemia.

#### *Psychiatric fatal case*

One case of suicide was reported, in a patient who had suffered from severe depressive episode after the birth of her previous child.

#### **Misuse**

The MAH of the originator product evaluated the compliance with the following dosing information based on the information reported in its database: 1.25mg of bromocriptine with food in the morning and evening on day 1, followed by 2.5mg twice a day for 14 days. Of the 5,184 AEs, 62.7% occurred under a daily dosing regimen in compliance with the PI, 217 AEs (4.2%) occurred under a daily dosing regimen not compliant with the PI and for 1,717 AEs (33.1%), the daily dose was not specified. With regards to the treatment duration, 41.5% of AEs occurred in compliance with the recommended treatment length while 4.7% of events occurred when treatment was over 14 days; this information was not available in 53.8% of AEs.

### **2.2.3. Published literature**

A Cochrane review (Oladapo, 2012 [3]) included 62 trials (6428 women) investigating the effectiveness of treatment used to prevent post-partum lactation. The trials were generally small and of limited quality and 22 trials did not contribute data that could be included in the meta-analysis. One of the primary outcome selected for the review was related to minor (nausea, vomiting, headache, dizziness) and major adverse events (thromboembolism, myocardial infarction and maternal death), however side effects were poorly reported in the trials and no case of thromboembolism was recorded in the four trials that reported it as an outcome.

#### **Pharmacoepidemiological studies**

Three observational studies investigated the risk of seizures, cardio- and cerebrovascular events, and hypertension related to bromocriptine.

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<sup>3</sup> Oladapo OT, Fawole B. Treatments for suppression of lactation. Cochrane Database Syst Rev. 2012 Sep 12;9:CD005937.

A record-based case-controlled study evaluated the relation between the use of bromocriptine to prevent lactation in the puerperium and the risk of post-partum seizure in 43 women who had a post-partum seizure and 319 matching controls. Overall, women taking bromocriptine had a 22% lower risk for seizures (RR 0.78; 90% CI 0.29 - 1.87). The authors found a small positive association between bromocriptine use and seizures occurring more than 72 hours after delivery (RR 1.6; 90% CI 0.37-6.08) further to control for seizure history. This association was offset by a strong negative association between bromocriptine use and early-occurring seizures. The pattern of an initial reduced risk followed by an increase to normal or above-normal levels of risk could result from an anti-seizure activity of bromocriptine, with a rebound in risk when bromocriptine is withdrawn (Rothman, 1990 [4])

A follow-up study performed among 2,130 women of 15-44 years of age who were treated with a course of bromocriptine for suppression of post-partum lactation in 1990-1992. None of these women were admitted to the hospital for cardiovascular or cerebrovascular events. However, the incidence of pregnancy hypertension and the use of cardiovascular drugs increased considerably in the last two months before delivery (Herings, 1995 [5]).

In a study to determine whether bromocriptine used for lactation suppression was a risk factor for post-partum hypertension, blood pressure was recorded at three visits between 3 and 21 days post-partum in 1813 women. Post-partum hypertension defined as systolic pressure of 140 mmHg or greater and/or diastolic pressure of 90 mmHg or greater on any of the three home visits, was the dependent variable; bromocriptine exposure was the independent variable. Covariates included age, race, chronic hypertension, pregnancy-induced hypertension, and antihypertensive medication. Discriminant analysis, including the first-order interactions, revealed that race, history of chronic hypertension, pregnancy-induced hypertension, and antihypertensive medication contributed significantly to post-partum hypertension ( $F(7, 1803) = 107.9; P < 0.001$ , explained variance 30%). Of all the interaction terms, only bromocriptine by pregnancy-induced hypertension interaction was significant (Watson, 1989 [6]).

### Case reports from the literature

Twenty-eight publications reported 44 cardiovascular cases, of which the most important were myocardial infarction, stroke, intracranial haemorrhages and hypertension. Risk factors were absent in the majority of women and the time of onset was relatively short.

Four psychiatric events were retrieved from three publications. In three of four patients no psychiatric history was present, the events started within a few days following the start of bromocriptine. In one case, a positive dechallenge was reported. In the remaining cases, treatment with haloperidol was initiated, and the symptoms quickly improved.

One publication reported seizures in relation to bromocriptine use, however no further information is available and no conclusion can be drawn. Another publication reported severe headaches and seizures in a woman with family history of pre-eclampsia (Makdassi 1991 [7]). The whole symptomology supported that bromocriptine was responsible for a general vasospasm. Hypertension resolved when bromocriptine was discontinued.

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<sup>4</sup> Rothman KJ, Funch DP, Dreyer NA. Bromocriptine and puerperal seizures. *Epidemiology*. 1990 May;1(3):232-8. Herings RM, Stricker BH. Bromocriptine and suppression of postpartum lactation. The incidence of adverse cardiovascular effects in women of child-bearing age. *Pharm World Sci*. 1995 Jul 28;17(4):133-7.

<sup>5</sup> Herings RM, Stricker BH. Bromocriptine and suppression of postpartum lactation. The incidence of adverse cardiovascular effects in women of child-bearing age. *Pharm World Sci*. 1995 Jul 28;17(4):133-7.

<sup>6</sup> Watson DL, Bhatia RK, Norman GS, Brindley BA, Sokol RJ. Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? *Obstet Gynecol* 1989;74:573-6.

<sup>7</sup> Makdassi R, de Cagny B, Lobjoie E, Andréjak M, Fournier A. Convulsions, hypertension crisis and acute renal failure in postpartum: role of bromocriptine? *Nephron*. 1996;72(4):732-3.

#### 2.2.4. Other pharmacovigilance activities

Two pharmacovigilance surveys were conducted in France including adverse events reported by pharmacovigilance regional centres and the MAH of the originator (included in the data presented above, see section 2.2.2), and covering the periods 1985-1993 and 1994-2010. In the first survey 53 cardiovascular and 36 neuropsychiatric cases, were identified representing 77% of the total of cases for an estimated exposure of 129,000 women per year in lactation inhibition. In the second survey conducted after the PI had been amended to minimise the risks observed previously, and more breastfeeding mothers were closely followed, 228 cases were retrieved including 105 serious cases for an estimated exposure of 147,000 women per year. In 66% of these serious cases, the use of bromocriptine was reported as not-compliant with the PI (e.g. dose increased too quickly, non-interruption of treatment despite precursor signs of neurologic or cardiovascular disorders, prescription in spite of increased risk factors) and this was identified as having possibly contributed to the appearance of the adverse events or their exacerbation. Among the 105 serious cases identified 70.5% corresponded to cardio and neurovascular disorders, 14.3% to nervous system disorders.

#### 2.2.5. Overall discussion on safety

The PRAC reviewed the safety results from all clinical studies conducted as part of the initial development plan and noted that no cardiovascular, neurological or psychiatric adverse events in association with post-partum administration of bromocriptine were observed.

The absolute number of cases reported in post-marketing is low, especially given the fact that bromocriptine has been available in the EU since 1973, with a substantial patient exposure; overall incidence rates are estimated to 0.005% to 0.04% (see table 1). The review of the fatal cases showed that risk factors were present in many of the cases where the information was available such as severe hypertension, hypertensive disorders of pregnancy, history of coronary artery disease or other cardiovascular condition as well history of psychiatric episodes. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances.

The analysis of case reports from the literature was hampered by the limited information available. However in some reports factors suggesting a possible causal association are present (no other risk factor or confounders, short time to onset (between 6 hours and 17 days after treatment initiation for the fatal cases where the information was available), positive de-challenge and re-challenge). From the pathogenic point of view, it is likely that vasospasm is responsible for these events.

No causal association was shown in the three observational studies investigating the risk of seizures, (Rothman, 1990 [8]) cardio- and cerebrovascular events, (Herings, 1995 [9]) and hypertension (Watson, 1989 [10]). Herings and colleagues concluded that, cardiovascular or cerebrovascular events observed could probably be explained by pre-existing morbidity rather than by the use of bromocriptine. The study observing the risks of hypertension found that while bromocriptine did not appear to increase the risk of inducing post-partum hypertension, it may aggravate already existing pregnancy-induced hypertension. Avoiding the elective use of this drug in patients with pregnancy-induced hypertension might constitute a reasonable clinical response to these findings. Based on a case report, it was recommended that familial history of preeclampsia should be included as a

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<sup>8</sup> Rothman KJ1, Funch DP, Dreyer NA. Bromocriptine and puerperal seizures. *Epidemiology*. 1990 May;1(3):232-8.

<sup>9</sup> Herings RM, Stricker BH. Bromocriptine and suppression of postpartum lactation. The incidence of adverse cardiovascular effects in women of child-bearing age. *Pharm World Sci*. 1995 Jul 28;17(4):133-7.

<sup>10</sup> Watson DL, Bhatia RK, Norman GS, Brindley BA, Sokol RJ. Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? *Obstet Gynecol* 1989; 74:573-6.

contraindication of bromocriptine in post-partum and for blood pressure to be closely monitored, especially in case of headaches (Makdassi, 1991 [11]).

Following assessment of all the data, the PRAC concluded the contraindications already in place in most Member States were valid and should be included in the PI across all MSs.

With regards to off label use and misuse, while high rates were reported in the French surveys, the analysis of the safety database of the MAH of the originator covering the period since the first marketing authorisation, focused on the dose and treatment duration, retrieved much lower rates (4.2% and 4.7% respectively). The second survey conducted in France retrieved a higher number of AEs, however this might not reflect an absolute increase in occurrence of those events but be the consequence of a change in post-marketing reporting of these events as more breastfeeding mothers were closely followed. Nevertheless, further information and awareness among the healthcare professionals is advisable to ensure safe use of the product. The PRAC recommends this information to be coordinated at individual Member States level. Moreover it was noted that at present the indication lactation inhibition in post-partum was also approved in high strengths, which should not be used for this indication. Indeed, as per the posology (see also 2.4) one dose given should not exceed 2.5 mg. For that reason the PRAC considered that to avoid medication errors or misuse of the products the indication of inhibition of lactation should be removed from the PI of the 5 mg and 10 mg strengths. This is considered an appropriate risk minimisation measure to reduce the misuse of the product.

It should be kept in mind that the post-partum is a vulnerable period with background risks of hypertension, convulsions, pre-eclampsia, psychiatric events and cardiovascular/cerebrovascular and thrombotic events. As compared with the non-pregnant state, the 6-week post-partum period is associated with a 3 to 9-fold risk of stroke, 3 to 6-fold risk of myocardial infarction, 9 to 22-fold risk of venous thromboembolic event and depression is estimated to occur in approximately 1 in 10 women while psychosis is estimated to occur in approximately 1-2 in 1000 women (Kittner, 1996 [12]; James, 2006 [13]; Salonen Ros, 2001 [14]; Heit, 2005 [15]; Jaigobin, 2000 [16]; James, 2005 [17]; Sultan, 2012 [18]). Furthermore, in part of the cases important risk factors (smoking, obesity, pre-eclampsia, hypertension, history of psychiatric episodes) were reported.

In conclusion, based on the available information a causal association between use of bromocriptine and serious cardiovascular, neurological or psychiatric events cannot be excluded. Therefore the PRAC recommended that safety information be included in the SmPC across the Member States.

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<sup>11</sup> Makdassi R, de Cagny B, Lobjoie E, Andréjak M, Fournier A. Convulsions, hypertension crisis and acute renal failure in postpartum: role of bromocriptine? *Nephron*. 1996; 72(4): 732-3.

<sup>12</sup> Kittner SJ, Stern BJ, Feaser BR, Hebel R, Nagey DA, et al. Pregnancy and the risk of stroke. *N Engl J Med* 1996 Sep; 335: 768-774

<sup>13</sup> James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation*. 2006 Mar 28; 113(12): 1564-71

<sup>14</sup> Salonen Ros H, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiology*. 2001 Jul; 12(4): 456-60.

<sup>15</sup> Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med*. 2005 Nov 15; 143(10): 697-706.

<sup>16</sup> Jaigobin C, Silver FL. Stroke and pregnancy. *Stroke*. 2000 Dec; 31(12): 2948-51.

<sup>17</sup> James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol*. 2005 Sep; 106(3): 509-16.

<sup>18</sup> Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. *Br J Haematol*. 2012 Feb; 156(3): 366-73

### **2.3. Pharmacodynamic**

Initiation of milk production starts after delivery and requires 2 to 5 days for the secretory maturation of acinar epithelium to occur. Although the initiation of lactogenesis depends on several hormones, the peripartum prolactin pulse has a major role, as its deletion results in a failure to initiate milk production. In the first week post-partum, the prolactin level declines by 50% (to about 100 ng/ml). Suckling results in increased level of prolactin, which is important for the maintenance of lactation. Up to 2-3 months post-partum, basal levels of prolactin are 40-50 ng/ml in the mother, with 10 to 20-fold increase upon suckling (Uvnäs-Moberg, 1990 [19]; Voogt, 2001 [20]; Peterson, 2014 [21]). These surges peak at levels of 100–200 ng/ml during the first week, 25–250 ng/ml during the second to fourth weeks, and less than 20–40 ng/ml thereafter, thereby indicating a continuous role for prolactin in lactation regulation and as a consequence a potential inhibitory action of bromocriptine in the late post-partum.

### **2.4. Clinical efficacy**

As part of this referral procedure, the MAHs were requested to provide all available data on the efficacy of bromocriptine in the prevention or suppression of physiological lactation from clinical studies and all other available data sources.

#### **2.4.1. Clinical studies**

Altogether 38 studies from the initial development programme were included in the development program for bromocriptine in lactation inhibition. These included 16 dose finding studies (484 patients), 10 comparative trials (394 patients) and 12 open trials (325 patients). Of these, 27 trials were conducted in the indication lactation prevention (726 women; trials 8-18, 24-31 and 34-41) and 11 in lactation suppression (220 women; trials 19-23, 32-33, 42-45).

#### **Dose finding studies**

Sixteen trials in 484 women were conducted to establish the optimum dose and treatment duration. In the 8 fixed dose prevention trials, women were given either 2.5 mg bromocriptine or 7.5 mg bromocriptine daily or placebo, for 7 days while in the 3 decreasing dose prevention trials women were given doses ranging from 7.5 mg daily for 14 days to 2.5 mg daily for 10 days with either a fixed dose or doses decreasing every 3 to 7 days. Results showed that 2.5 mg were practically as effective as 7.5 mg, both dosages were very well tolerated, and that extending treatment duration from 7 to 14 days resulted in a decrease of relapses, the optimum dosage regimen was found to be 2.5 mg twice daily for 14 days.

In the five decreasing dosage suppression studies women were administered 5 mg daily for 14 days followed by either placebo or 2.5 mg daily for an extra 7 days, starting between 3.6 days to 13.8 post-partum in 66 women and between 6.1 to 16.7 weeks post-partum in 35 women. Results did not show enough evidence in favour a third week of treatment and the same dosage regimen was retained.

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<sup>19</sup> Uvnäs-Moberg K, Widström AM, Werner S, Matthiesen AS, Winberg J. Oxytocin and prolactin levels in breast-feeding women. Correlation with milk yield and duration of breast-feeding. *Acta Obstet Gynecol Scand.* 1990;69(4):301-6.

<sup>20</sup> Voogt JL, Lee Y, Yang S, Arbogast L. Regulation of prolactin secretion during pregnancy and lactation. *Prog Brain Res.* 2001;133:173-85.

<sup>21</sup> Peterson CM. Prolactin: Physiologic and Pathologic Associations. In: Peterson CM. *Human Reproduction: Clinical, Pathologic and Pharmacologic Correlations*, 1997.

## Comparative trials

Ten double blind trials were conducted comparing bromocriptine against other anti-galactic agents, 3 oral oestrogens and a controlled-release formulation of oestrogens and progesterone in injectable form. Of the total 394 patients included in the 10 trials, 198 were treated with the pre-established dosage regimen of bromocriptine, 2.5mg twice daily, (8 prevention trials and 2 suppression trials) and 196 with reference products, either diethylstilbestrol, chlorotrianisene, methallenestril or an injectable fixed combination of estradiol, norethindrone and testosterone.

The efficacy of treatments was evaluated using overall assessment of treatment by physician, patient or midwife, mammary secretion, congestion, breast engorgement, possible return of mammary secretion after stopping treatment.

Bromocriptine performed better than the comparator drugs in the 8 prevention trials (319 patients). Bromocriptine was significantly superior to 3 of the comparator drugs in 236 cases and equal to methallenestril (83 patients). Its efficacy was assessed as good in 88%, 98% and 100% (compared with chlorotrianisene, diethylstilbestrol and methallenestril /the estradiol, norethindrone and testosterone combination, respectively) and as moderate in 96% of 160 cases. In contrast, the efficacy of the reference products was good in 42% of cases for chlorotrianisene and in 90% for methallenestril. Cases of serious relapses requiring treatment were observed approximately twice as frequently with the reference products as with bromocriptine (11% vs. 6%). The percentage of women in with mammary secretion and congestion was in all cases lower with Bromocriptine than with the comparator drugs.

There were no major differences between bromocriptine and the comparator drugs diethylstilbestrol and methallenestril in the 2 suppression trials, except for one trial where the total number of relapses was much lower with bromocriptine than with diethylstilbestrol (trial 32; 5 out of 20 vs. 16 out of 19). In the trial comparing bromocriptine to methallenestril, women were started on lactation inhibition treatment around 6 and 9 days post-partum, respectively.

## Open trials

Twelve open trials were conducted in an analogue way to the comparative trails. In the eight open trials conducted in prevention, overall efficacy was assessed as good in 89% of the 244 cases evaluated. In the four open trials performed in suppression, where this information was available (in 35 women) treatment was started around 6 or 40 days post-partum and was judged as effective in 74% of the 79 evaluated cases.

## Post-authorisation studies

Four studies were conducted later, in the following indications: painful breast engorgement, incipient mastitis, and prevention of post abortion lactation; these studies are summarised below:

Painful breast engorgement: a single dose of 2.5 mg Bromocriptine was administered to 36 women and followed by a second dose if symptoms persisted. In 28 out of 36 women, relief of pain and regression of engorgement was reported after the first dose. In 6 cases, a second dose was required. Two patients failed to respond to therapy within 24 hours and treatment was continued with 5 mg daily for 14 days. In the 9 cases where prolactin levels where recorded, a rapid and significant fall in plasma prolactin was observed after 6 hours of drug administration ( $p < 0.001$ ) followed by a rapid return of plasma prolactin to pre-treatment levels upon treatment discontinuation.

Incipient mastitis: two open trials were conducted in this indication. In the first trial, 32 out of 35 women reported relief of pain and breast engorgement. Local signs of inflammation rapidly subsided

and temperature normalised within 12-24 hours. The results indicate that in over 90% (32 out of 35), the relief of milk stagnation with bromocriptine alone prevented the progression of inflammation to abscess formation without antibiotic coverage. In the second study, 1.25 mg of bromocriptine was administered three times daily in addition to antibiotics and physical therapy. In 26 of the cases, rapid decrease of inflammation signs and normalisation of temperature and white cell count were observed.

Prevention of post-abortion lactation: fifty women were treated with either 2.5 mg of bromocriptine twice daily for 14 days and compared to an equivalent untreated group. In the group of untreated controls, spontaneous milk secretion occurred in 22% and persisted for several days. In the group of bromocriptine- treated women, only one case exhibited lactation with moderate production of milk which diminished gradually.

## 2.4.2. Literature data

Analysis of the published literature retrieved a number of clinical trials, with a majority conducted before the 1990.

From the Cochrane review by Oladapo and colleagues (see also above section 2.2.3) three trials in 107 women indicated that bromocriptine significantly reduced the proportion of women lactating compared with no treatment within seven days post-partum (three trials, 107 women; risk ratio (RR) 0.36, 95% confidence interval (CI) 0.24 to 0.54). However, in two studies, on post-partum day 14 bromocriptine was not more effective than the placebo (RR 0.18; 95% CI 0.03 - 1.08). Ten double-blind comparative studies indicated that the use of bromocriptine is superior in both preventing and suppressing puerperal lactation as compared to synthetic oestrogen treatments, androgens, combined oral contraceptive, pyridoxine. Trials comparing bromocriptine with other pharmacologic agents such as methergoline, lisuride, prostaglandins, pyridoxine, cabergoline, diethylstilbestrol, cyclofenil and a non-ergot dopamine agonist suggested similarity in their effectiveness. No trials were presented comparing non-pharmacologic methods with no treatment. Four trials suggested similarity in the risk of rebound lactation between bromocriptine and other pharmacologic agents including lisuride (RR 0.65; 95%CI 0.39 - 1.10), whereas rebound rate was found higher for bromocriptine than cabergoline in another study.

Other studies suggested that bromocriptine was more effective than cyclofenil (O'donoghue, 1977 [22]), diethylstilbestrol ((Nilsen, 1976 [23]), androgen (Biggs, 1978 [24]), non-pharmaceutical method (ice and tight bra) (Wong, 1985 [25]) and tiopronin (Akrivis, 2010 [26]). Two studies suggested that bromocriptine might have a higher rate of relapse compared to cyclofenil (O'donoghue, 1977 and Thorbert, 1983 [27]) and lisuride (Van dam, 1981 [28]).

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<sup>22</sup> O'Donoghue RF. The suppression of puerperal lactation with bromocriptine. *Irish Medical Journal* 1977; 70(5): 172-3.

<sup>23</sup> Nilsen PA, Meling AB, Abildgaard U. Study of the suppression of lactation and the influence on blood clotting with bromocriptine (CB 154) (Parlodel): a double blind comparison with diethylstilbestrol. *Acta Obstetrica et Gynecologica Scandinavica* 1976; 55: 39-44.

<sup>24</sup> Biggs JS, Hacker N, Andrews E, Munro C. Bromocriptine, methyl testosterone and placebo for inhibition of physiological lactation: a controlled study. *Medical Journal of Australia* 1978; 2(3 Suppl): 23-5.

<sup>25</sup> Wong S, Stepp-Gilbert E. Lactation suppression. Nonpharmaceutical versus pharmaceutical method. *J Obstet Gynecol Neonatal Nurs.* 1985 Jul-Aug; 14(4): 302-10.

<sup>26</sup> Akrivis C, Vezyraki P, Kiortsis DN, Fotopoulos A, Evangelou A. Inhibition of puerperal lactation with 2-mercaptopyrionyl-glycine. *Eur J Clin Pharmacol.* 2000 Dec; 56(9-10): 621-3.

<sup>27</sup> Thorbert G, Akerlund M. Inhibition of lactation by cyclofenil and bromocriptine. *British Journal of Obstetrics and Gynaecology* 1983; 90: 739-42.

<sup>28</sup> Van Dam LJ, Rolland R. Lactation-inhibiting and prolactin lowering effect of lisuride and bromocriptine: a comparative study. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1981; 12: 323-30

### **2.4.3. Overall discussion on efficacy**

Although most of the studies conducted with bromocriptine are conducted before 1990, the available evidence from clinical trials conducted as part of the original clinical development plan as well as from the published literature suggests that bromocriptine is efficacious in the indication currently under review and appeared superior to androgens, combined contraceptives, anti-oestrogens, pyridoxine, and of similar efficacy than that of other dopamine agonists, though possibly better than lisuride. In some studies bromocriptine was associated with higher incidence of rebound phenomenon compared to cabergoline (in one study), and similar to lisuride or non-ergot dopamine agonist.

In the clinical trial assessing the efficacy of bromocriptine in late post-partum, treatment was initiated at times covering adequately the late post-partum period (10 to 13.8 days post-partum and 38.9 days to 16.7 weeks post-partum). Considering the mechanism of regulation of lactation and the results of these studies the PRAC considered the efficacy of bromocriptine in lactation inhibition sufficiently demonstrated.

However, although the studies conducted in mastitis, breast engorgement and painful breast engorgement suggested some efficacy, the limited data available does not allow concluding on the efficacy of bromocriptine in these indications. The PRAC concluded that these should not be mentioned in the PI as examples of situations where bromocriptine could be used.

In addition, as one dose administered should not exceed 2.5 mg in this indication, in order to minimise the risk of misuse and medication error, the indication prevention or suppression of lactation should be removed from the product information of the higher strengths (see also section 2.2).

### **2.5. Overall benefit-risk assessment**

The PRAC reviewed the efficacy and safety data following oral treatment with bromocriptine in post-partum inhibition of lactation, in particular data related to the risk of cardiovascular, vascular neurological and psychiatric adverse events.

A range of adverse events have been reported, including depression, psychosis, myocardial infarction, stroke, intracranial haemorrhage, thrombotic events, convulsions and hypertension. Overall, considering the substantial exposure to this active substance, the PRAC considered the number of cases as low. Although some factors suggested causality of the events to bromocriptine, independent risk factors for these types of events are present in the post-partum period. Based on the available data the PRAC could not exclude a causality between the use of bromocriptine and cardiovascular, neurovascular and psychiatric events; these are already included in many PI for these products.

Clinical studies and published literature supported the use of bromocriptine in prevention or suppression of physiological lactation in post-partum. However, although some efficacy was suggested in the treatment of mastitis and painful breast engorgement, these studies were limited and did not constitute sufficient evidence to support including these situations as examples in the indication.

The PRAC was of the opinion that this potential risk could be mitigated through limiting the use of bromocriptine to circumstances where breastfeeding is not possible due to medical reasons (such as intrapartum loss, neonatal death, HIV infection of the mother) and inclusion of contraindications, warning and precautions in the product information, as it is already the case in some Member States.

Following the assessment of the relevant data, the PRAC recommended not to use bromocriptine for the routine suppression of lactation or for the relief of symptoms of post-partum pain and engorgement which can be adequately treated with non-pharmacological intervention (such as firm breast support, ice application) and/or simple analgesics.

In addition, the PRAC was of the view that the contra-indication in patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium, and patients with a history of coronary artery disease or other severe cardiovascular conditions, or symptoms/history of severe psychiatric disorders, already partially in place in most Member States should be implemented across all Member States.

The PRAC recommended that blood pressure should be closely monitored, especially during the first days of therapy and a warning advising to discontinue treatment in case of hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of central nervous system toxicity, and that this should be reflected in the product information.

In addition, the PRAC considered that, to avoid medication errors or misuse, the indication for post-partum inhibition of lactation, should be removed from the product information of the 5 mg and 10 mg strengths.

Finally, the PRAC considered that further information and awareness among the healthcare professionals was advisable. This information can be coordinated at individual Member States level in order to raise prescribers' awareness of the main points included in the product information, in particular that the product should only be used when medically indicated while monitoring periodically blood pressure and that it is contraindicated in women with existing or with a history of cardiovascular, neurologic and psychiatric disease as detailed below in section 2.6.

Based on these conclusions, the PRAC concluded that the benefit-risk balance of bromocriptine-containing medicinal products remains favourable subject to changes to the product information, including agreed restrictions and warnings.

## **2.6. Changes to the product information**

The PRAC recommended that amendments be introduced in the Summary of Product Characteristics (SmPC) to sections 4.1 Therapeutic indications, 4.3 Contraindications, and 4.4 Warnings and precautions of use; of note, some are already included in of the PI of the products in Members States:

- An amendment of section 4.1 which includes a recommendation that bromocriptine should only be used to inhibit lactation when medically indicated such as in case of intrapartum loss, neonatal death and HIV infection of the mother. In addition this section should recommend against the use of bromocriptine for the routine suppression of lactation or for the relief of symptoms of post-partum pain and engorgement which can be adequately treated with non-pharmacological intervention (such as firm breast support and application of ice) and/ or a simple analgesics. Moreover this indication should not appear in the product information of strengths above 2.5 mg in order to minimise the risk of misuse or medication error.
- In section 4.3 for all medicinal products included in this review a contraindication should be included for patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium, a history of coronary artery disease or other severe cardiovascular conditions, or symptoms / history of severe psychiatric disorders.
- In section 4.4 a warning should be included indicating that blood pressure should be carefully monitored especially during the first day of therapy as, in rare cases, serious adverse events (e.g. hypertension, myocardial infraction, seizures, strokes or psychiatric disorders) have been reported

in post-partum women treated with bromocriptine for the inhibition of lactation. In addition, if hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbance) or evidence of central nervous system toxicity develops, treatment should be discontinued and the patient evaluated promptly.

Corresponding changes to the package leaflet have also been introduced.

### 3. Overall conclusion and grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for bromocriptine-containing medicinal products for oral use in the post-partum inhibition of lactation;
- The PRAC reviewed all available data from post-marketing spontaneous case reports, clinical trials, published literature and other available information on bromocriptine-containing medicines for oral use with regards to the cardiovascular, neurological and psychiatric risk following treatment in post-partum lactation inhibition. The PRAC considered the relation between the use of bromocriptine-containing medicinal products for oral use in post-partum inhibition of lactation and the occurrence of serious cardiovascular, neurological and psychiatric adverse events. The PRAC also considered the available data on the efficacy of these products;
- The PRAC recommended to limit the use of bromocriptine-containing medicinal products for oral use in the post-partum inhibition of lactation with strength of 1 mg and 2.5 mg to cases where medically indicated. In addition the use of these products is not recommended for routine suppression of lactation or for relief of symptoms of post-partum pain and engorgement which can be adequately treated with non-pharmacological intervention or with analgesics. Furthermore the blood pressure of patients should be carefully monitored. If any symptoms of hypertension or evidence of central nervous system toxicity are detected, the administration of bromocriptine should be discontinued;
- In addition, the PRAC recommended all strengths of these products to be contraindicated in patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and puerperium as well as in patients with a history of coronary artery disease or other severe cardiovascular conditions, or symptoms/history of severe psychiatric disorders;
- Finally, for the bromocriptine-containing medicinal products for oral use in the post-partum inhibition of lactation with the strengths of 5 mg and 10 mg, the PRAC is of the opinion that the benefit does not outweigh the risks of misuse and medication error and therefore recommended this indication to be deleted.

Having considered the matter, the PRAC therefore recommended the variation of the marketing authorisations for bromocriptine-containing medicinal products for oral use indicated in the post-partum inhibition of lactation.

The divergent positions are appended to this report.

# Appendix 1

## *Divergent positions*

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1379

Bromocriptine-containing medicinal products for oral use indicated in post-partum inhibition of lactation

INN: bromocriptine

### **Divergent statement**

The undersigned members of the PRAC do not agree with the PRAC recommendation on the variation to the Marketing Authorisation of oral bromocriptine-containing products authorised for inhibition of lactation.

Despite these members are in agreement with the following scientific points highlighted by the PRAC and based on the rapporteur's and co-rapporteur's reports, i.e. they agree that:

- bromocriptine efficacy for lactation inhibition or suppression in the immediate post-partum is demonstrated;
- the role of bromocriptine in serious and fatal cases of cardiovascular, cerebrovascular, neurologic and psychiatric disorders occurred with bromocriptine cannot be ruled out;
- a high number of reported cases of use failed to comply with the contraindications, warnings and posology of the bromocriptine containing-products;
- wording of section 4.1 of the EU SmPCs are not harmonised;
- wording of sections 4.3, 4.4 and 4.8 of the EU SmPCs are not harmonised;

the reasons for this divergent opinion rely on a disagreement with the proposed regulatory actions, focused on the indication and the risk minimisation measures adopted and were as follows:

- physiological nature of post-partum lactation, which ceases in one to two weeks if the infant is not put to the breast;
- bromocriptine efficacy for lactation inhibition in the late post-partum period has not been demonstrated and bromocriptine use is not pharmacologically justified due to the physiological lactation process;
- use for "medical reason only" is already mentioned in most of indication section of the EU SmPCs.
- risks of cardiovascular, cerebrovascular, neurologic and psychiatric disorders are already described in EU SmPCs;
- reinforcement of the SmPC in France in 1994 of the bromocriptine containing-products was insufficient to limit cardiovascular, cerebrovascular, neurologic and psychiatric disorders and misuse;
- withdrawal of bromocriptine in the indication lactation inhibition in Canada in 1994 and by the FDA in 1995 for safety concerns (mainly cardio and neuro-vascular events), followed by Italy and some Arabic countries;
- alternative pharmacological treatments are authorised in Europe.

Taking all these aspects into account, the undersigned members of the committee considered that risk minimisation measures proposed by the PRAC (e.g. amendments and harmonisation of the bromocriptine containing-products SmPCs through EU) are not sufficient to mitigate the risks of cardiovascular, cerebrovascular, neurologic and psychiatric disorders associated with the oral use of bromocriptine in post-partum inhibition of lactation and therefore considered that the benefit/risk ratio of bromocriptine in this indication is negative. Thus, they propose the withdrawal of all oral bromocriptine-containing products authorised in this indication.

**PRAC members expressing a divergent opinion:**

Carmela Macchiarulo (IT)	10 July 2014	Signature: .....
Isabelle Robine (FR )	10 July 2014	Signature: .....