Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

The CMDh, having considered the PRAC recommendation dated 10 July 2014 with regards to the bromocriptine containing medicinal products, agrees with the recommendation therein as stated below:

Overall summary of the scientific evaluation of bromocriptine containing medicinal products (see Annex I)

Bromocriptine is used to prevent or suppress lactation in women who have given birth. In 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.

In the mid-1990s the indication of lactation was withdrawn in the United States and some other countries in view of reports of cardiovascular adverse events (AEs) in women treated with bromocriptine-containing products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.

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Directive 2001/83/EC, on whether marketing authorisations of these products should be maintained, varied, suspended or withdrawn.

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%. 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) cardio- and cerebrovascular events, (Herings, 1995) and hypertension (Watson, 1989). 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 contraindication of bromocriptine in post-partum and for blood pressure to be closely monitored, especially in case of headaches (Makdassi, 1991).

Following assessment of all the data, the PRAC concluded the contraindications already in place in most Member States (MSs) were valid and should be included in the PIs 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. This information can 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 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 infraction, 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. 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.

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 product information 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.

Benefit-risk balance

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.

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

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.

Grounds for the PRAC 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.

Therefore, in accordance with Articles 32 of Directive 2001/83/EC, the PRAC recommends the variation to the terms of the marketing authorisations, for all medicinal products containing bromocriptine

identified in Annex I and for which the amendments to the product information are set out in Annex III of the PRAC recommendation.

The PRAC, as a consequence, concluded that the benefit-risk balance of oral bromocriptine-containing medicinal products in the post-partum inhibition of lactation identified in Annex I remains favourable, subject to the agreed changes to the product information including restrictions and warnings.

CMDh position

The CMDh having considered the PRAC recommendation dated 10 July 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached a position on the variation to the terms of the marketing authorisations of bromocriptine-containing medicinal products for oral use indicated in post-partum inhibition of lactation for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III.