Annex II

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

Scientific conclusions

Overall summary of the scientific evaluation of Oxynal and Targin and associated names (see Annex I)

Background

Oxynal 10mg/5mg, 20mg/10mg prolonged-release tablets and Targin 5mg/2.5mg, 10mg/5mg, 20mg/10mg, 40mg/20mg prolonged-release tablets and associated names (OXN PR) are fixed combination products of oxycodone hydrochloride and naloxone hydrochloride. OXN PR is currently indicated in “severe pain, which can be adequately managed only with opioid analgesics”.

On 31 August 2012, the MAH submitted a type II variation via the mutual recognition procedure (MRP) for Oxynal and Targin and associated names, to request the inclusion of “symptomatic treatment of patients with moderate to severe idiopathic restless legs syndrome insufficiently treated with dopaminergic therapy”. During the CMD(h) referral procedure, the proposed restless legs syndrome indication was restricted to “second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy".

As the reference and concerned member states were not able to reach an agreement in respect of the variation, on 2 May 2014, Germany triggered a referral under Article 13(2) of Regulation EC No 1234/2008.

On the basis of the questions raised by the Netherlands the points to be considered by the CHMP were:

1. There is a lack of confirmatory evidence regarding the maintenance of efficacy and the long-term safety, which has not been provided by the open-label extension study phase, due to its methodological limitations.

No convincing scientific evidence has been provided in the perspective of public health that the benefit of the fixed dose combination of oxycodone/naloxone in the treatment of idiopathic restless leg syndrome (IRLS) outweighs the expected adverse effects that are associated with the use of strong-opioids in doses equipotent to doses up to 90 mg of oral morphine; dependence, withdrawal, augmentation, misuse and abuse.

2. The available clinical data of only one single, short term, pivotal trial are considered insufficient considering the risks. Therefore, further justification that the different criteria for approval on the basis of one pivotal trial should be provided by the applicant.

Scientific discussion

Efficacy

In order to demonstrate the efficacy and safety of OXN PR in the symptomatic treatment of patients with moderate to severe idiopathic restless legs syndrome insufficiently treated with dopaminergic therapy, the application dossier was based on a pivotal phase III clinical study (No OXN 3502) and open label extension study phase (No OXN 3502S).

The results of the pivotal phase III clinical study are considered robust and consistent with respect to primary and secondary efficacy parameters (addressing severity and impact of the disease and quality of life) as well as with respect to responder rates and various subgroup analyses.

Even using a very conservative statistical approach, the magnitude of effect (decrease in mean IRLS of 5.9 points compared to placebo) was in line with or even slightly better than the results found in the placebo-controlled studies with dopamine agonists approved as first line treatment.

Therefore, short term efficacy of OXN PR as second line treatment of severe to very severe RLS after failure of dopaminergic treatment has convincingly been shown in the pivotal study OXN3502.

The maintenance of treatment effect was investigated in the open extension phase of the pivotal study. 97% of patients completing the double-blind controlled study entered the extension phase. The results at the end of the extension phase at week 52 showed a further slight improvement of the IRLS sum score compared to the results towards the end of 12-week double-blind phase. The mean ILRS score at the end of the open extension study was 9.72 and corresponds to a mild symptom severity. The treatment effect during the extension phase was independent from treatment during the pivotal study.

In addition, further improvements in the patient's condition by the end of the extension phase compared to the end of the double-blind phase was observed in the secondary efficacy parameters, including reduction in the severity of illness, improvements in sleep, RLS related pain and quality of life, respectively.

The CHMP noted that the mean daily dose of OXN PR used in the extension phase was almost identical (and even slightly lower) compared to the mean daily dose used in the double-blind phase (18.12 mg vs. 22.62 mg), with no difference in mean doses in the extension phase between the subgroups previously treated with OXN PR or placebo.

The CHMP acknowledged the methodological limitations of the open label study however the CHMP considered that reasonable justifications for maintenance of effect up to 52 weeks of treatment were provided by the MAH.

The CHMP noted that there is evidence from the literature that the endogenous opioid system is involved in the pathogenesis of RLS on a spinal and supraspinal level and therefore there is a plausible rationale to justify the use of opioids for treatment of RLS [1,2]. In addition, the CHMP highlighted the unmet medical need in the treatment of severe to very severe RLS.

Safety

A detailed review of safety data from both the double-blind phase and extension phase (OXN3502/S) was conducted.

The frequency of adverse events and related adverse events was mostly comparable for both study phases (OXN3502/S) and points to a better tolerability of OXN PR in the extension phase. The safety profile was also considered to be in-line with the experience of OXN PR used for the treatment of pain where adverse events are also more frequently reported at the beginning of therapy. There were no notable differences in the frequency of adverse events, severe adverse events and serious adverse events (overall and treatment-related) for young vs. elderly subjects as well as for females vs. males.

No case of augmentation, tolerance, psychological dependence (addiction), abuse or misuse was reported in the studies OXN3502/S.

The review of 'opioid dependence' revealed that during the extension phase two reports of withdrawal symptoms were obtained as part of the standard adverse event reporting procedures. Further 10 patients out of 176 reported signs of physical dependence as a result of a specific follow-up visit 4 weeks after the end of the extension phase. However, the protocol did not stipulate dose tapering and in the majority of these subjects no tapering had been performed.

These findings are in line with the results of the post-marketing surveillance with OXN PR in the treatment of pain where addiction and related abuse are carefully monitored.

[1] Walters AS et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep 1993; 16: 327-332.
[2] Walters AS et al. The MU Opiate Receptor Knock-out Mouse Shows Increased Sensitivity to Pain, Increased Motor Activity During the Sleep Period and Decreased Serum Iron Parallel to Human Restless Legs Syndrome. Sleep 2011; 34: A199.

The CHMP agreed that the risk of physical dependence and associated withdrawal reaction can be mitigated and adequately managed by the strengthened tapering advice proposed.

Based on clinical experience and clinical guidance, the potential abuse and misuse of opioid analgesics in the controlled pain therapy is considered low. Compared to other opioids, a lower potential for psychological dependence and abuse is further expected with OXN PR, as it is a prolonged release formulation whereas it is currently accepted knowledge that the risk of psychological dependence increases with faster drug release. Furthermore, the risk of parenteral or intranasal misuse of OXN PR by individuals dependent on opioid agonists is expected to be low as marked withdrawal symptoms are expected due to the opioid receptor antagonist characteristics of naloxone.

Therefore, the CHMP endorsed that the use OXN PR as a prolonged-release formulation of oxycodone and naloxone reduces the risk of abuse or misuse.

In addition, in order to further increase safety and appropriate use of OXN PR in the IRLS indication, the maximum daily dose has been limited to 60 mg/day. The CHMP is of the opinion that the mean daily dose of 20mg/10mg oxycodone hydrochloride/naloxone used in the pivotal trial and being considerably lower than the doses needed in the pain indication should be mentioned in the SmPC to guide dosing. The RLS treatment with OXN PR should be supervised by a clinician with experience in the management of IRLS.

Treatment with OXN PR in RLS has been contraindicated in patients with a history of opioid abuse. Warning regarding somnolence/sleep attacks and ability to drive/operating machinery has been added to the product information in accordance with the information given in the respective product information of dopaminergic substances approved in the RLS indication.

In addition, clear instructions have been proposed for section 4.2 of the SmPC to re-evaluate the benefits and risks in individual RLS patients regularly every 3 months and to consider a discharge regimen by gradual tapering before treatment is continued beyond 1 year.

Further caution is included in the section 4.4 of the SmPC when OXN PR is administered to elderly irrespective of the indication.

As requested during the CMDh procedure, the applicant has further made a commitment to perform a drug utilisation study (DUS) and to update the risk management plan (RMP) subsequently to approval of the DUS in order to address concerns based on uncertainties that data of the clinical study including the long-term extension might not fully characterise a possible risk of tolerance, dependence and drug abuse in long-term use in IRLS.

Conclusion

The CHMP considered that the data provided by the MAH are sufficient to support the use of Oxynal and Targin and associated names in the second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy. The CHMP also took note of the risks of iatrogenic drug dependence, drug abuse or misuse, augmentation, tolerance, and psychological dependence associated with Oxynal and Targin and associated names. Overall, the CHMP considered that benefits of Oxynal and Targin and associated names in the sought indication outweigh the risks, taking into account the additional risk minimisations measures which had already been agreed at CMD(h) and the changes recommended to the product information.

Grounds for the variation to the terms of the marketing authorisation with amendments to the relevant sections of the summary of product characteristics

Whereas

- The Committee considered the referral under Article 13(2) of Regulation No 1234/2008.
- The Committee reviewed all available data in support of the safety and efficacy of Oxynal and Targin and associated names in “second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy”.
- The Committee considered that the data of the pivotal phase III study and extension phase part are supportive of short term and long term efficacy of Oxynal and Targin and associated names in the second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy.
- The Committee considered that the amendments to the product information are appropriate to mitigate the risks of iatrogenic drug dependence, drug abuse or misuse, augmentation, tolerance and psychological dependence. A drug utilisation study will also be conducted to further characterise a possible risk of tolerance, dependence and drug abuse in long-term use in idiopathic restless leg syndrome.
- The Committee concluded, in view of available data, that the benefit risk of Oxynal and Targin and associated names for “second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy” is positive.

Therefore, the Committee recommended the granting of the variation to the terms of the marketing authorisations for the medicinal products referred to in Annex I, for which the valid summary of product characteristics, labelling and package leaflets remain as per the final versions achieved during the Coordination group procedure with amendments as mentioned in Annex III.