EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 13(2) of Regulation EC No 1234/2008

Oxynal-Targin and associated names

INN/active substance: oxycodone hydrochloride / naloxone hydrochloride

Procedure number: EMEA/H/A-13/1402

Note
Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 31 August 2012, Mundipharma GmbH submitted an application for Oxynal and Targin and associated names through a mutual recognition procedure (MRP) type II variation (DE/H/XXXX/WS/044) with Germany acting as Reference Member State (RMS). The Concerned Member State (CMS) were: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, and United Kingdom.

The applied variation was to include “Second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy” in addition to the approved indication “Severe pain, which can be adequately managed only with opioid analgesics.”

The type II variation procedure started on 15 November 2012. Since no agreement was reached between the RMS and the CMS the procedure was referred to Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD(h)) by Germany on 5 February 2014. The CMD(h) 60 day procedure was initiated on 4 March 2014.

Day 60 of the CMD(h) procedure was on 2 May 2014, and since there could be no agreement the procedure was referred to CHMP.

On 2 May 2014, Germany triggered a referral under Article 13(2) of Regulation EC No 1234/2008. The CHMP was requested to give its opinion on whether the variation for medicinal products containing Oxynal-Targin and associated names should be granted or refused.

2. Scientific discussion

2.1. Introduction

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. Oxycodone is a semi-synthetic opioid which is a narcotic analgesic generally indicated for relief of moderate to severe pain. Naloxone is a pure opioid antagonist which is generally used to counter the effects of opioid overdose. In this case, it added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

OXN PR is currently indicated in “severe pain, which can be adequately managed only with opioid analgesics”.

In the variation procedure the MAH applied for OXN PR to be used in “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".

Following the CMD(h) 60 day procedure, the Netherlands was of the opinion that the benefit risk balance of OXN PR for the restricted indication is still considered negative. The available clinical data, the proposed adapted product information and the proposed risk minimisation measure are insufficient to assure that the risks of iatrogenic drug dependence and drug prescription abuse outweigh the

benefits. In addition, the fact that no case of psychological dependence or tolerance was reported during the studies raises some doubts about the monitoring of these expected adverse effects.

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.

2.2. Clinical 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 pivotal study (No OXN 3502) was a 12-week randomised double-blind, double-dummy, placebo-controlled study. The study comprised three phases: a pre-randomisation phase that included a 7-10 days wash-out phase, a 13 weeks double-blind phase and a 40 weeks open-label extension phase. Patients with at least moderate idiopathic restless leg syndrome (IRLS score $\geq$ 15) at screening despite current or previous treatment were included.

After randomisation, patients started either on OXN PR 5/2.5 mg twice daily or placebo respectively. The subject's study medication dose could be titrated every 7 days up to OXN PR 40/20 mg twice daily.

The primary endpoint was the improvement of symptom severity of restless leg syndrome (RLS) measured by the IRLS total score.

The most relevant secondary efficacy variables to assess the clinical benefit of OXN PR in RLS were:

- Improvement of severity of RLS in the Clinical Global Impression (CGI) severity scale
- Change of severity of RLS during the day at rest (RLS-6-Rating Scale)
- Quality of Life – Restless Legs Scale (QoL-RLS-Scale)
- Medical Outcomes Study (MOS) sleep scale
- Numeric Rating Scale (NRS) for RLS pain

Patients included in the study had RLS symptoms on average for more than 10 years, only 5 % suffered from RLS symptoms for less than 1 year. Patients had already been treated with a variety of medicinal products and previous treatment lasted on average 60 months. The duration of the last treatment before study entry was on average 25 months. More than 50% had their last treatment for more than a year. The majority of the patients of OXN3502 were on dopaminergic treatment at start of the study.

The main objectives of the extension study phase (No OXN 3502S) were to:

- Assess the tolerability and long-term safety of OXN PR in subjects with restless leg syndrome;
- Demonstrate maintenance of treatment effect up to 52 weeks;
- Evaluate the potential of OXN PR to prevent the development of augmentation, a major complication of restless leg syndrome long-term treatment with dopaminergic agents.

2.2.1. Results

Pivotal phase III clinical study (No OXN 3502):

Primary endpoint

The primary efficacy endpoint as measured by the internationally accepted and used IRLS sum score showed statistically significant superiority of OXN PR to placebo (8.15 units according to the pre-defined primary statistical analysis ($p<0.001$) and 7.2 units using ANCOVA LOCF ($p<0.001$)). Even using a very conservative statistical approach (placebo dropouts considered like placebo mean responders) the IRLS sum score for OXN PR was still 5.9 units superior to placebo ($p<0.001$). The ANCOVA LOCF analysis method is comparable to the methods used for dopaminergic agents and therefore allows a meaningful comparison.

Even when applying the very conservative statistical approach the result obtained with OXN PR is well in the range of results of dopaminergic treatment (2.5 to 6.9 units).

The effect size of 0.63 (applying the ANCOVA LOCF calculated treatment effect of 7.2) for OXN PR reflects a moderate treatment effect and is at the upper end of effect size values demonstrated for dopaminergic agents (0.29 to 0.66).

Secondary efficacy parameters

All secondary efficacy parameters (addressing severity and impact of the disease and quality of life), subgroup analyses (single dose groups, pre-treatment including quantitative (number of treatments) and qualitative aspects (dopaminergic substances classes), gender and secondary endpoints) and responder rates are consistent with the primary efficacy results.

Extension study phase (No OXN 3502S):

Maintenance of treatment effect for up to 52 weeks was investigated in the open extension part of the pivotal study.

The results at the end of the open extension phase at week 52 showed a further slight improvement of the IRLS sum score compared to the results towards the end of the 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 double-blind phase (Figure 1).

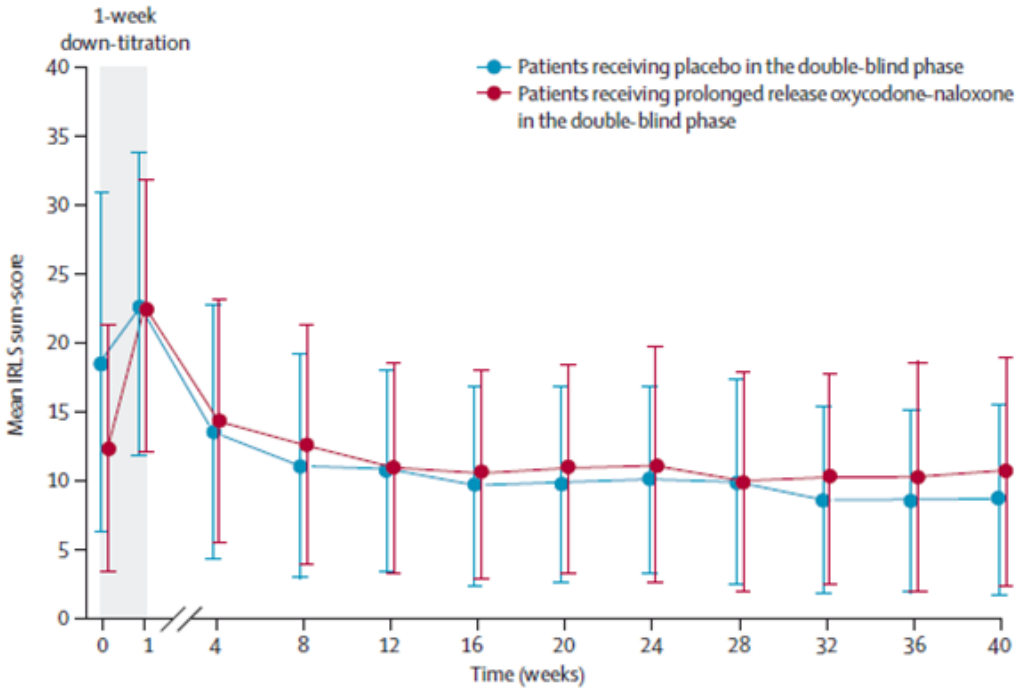
A lower number of subjects discontinued in the double-blind phase compared to a higher number of subjects in the placebo group who discontinued due to lack of therapeutic effect (OXN PR 6.7% vs. 19.5% Placebo).

The discontinuation rate in the extension phase was approximately 20%. However, in only 3% the reason for premature withdrawal was given as lack of therapeutic effect. The dropout rates observed in

the pivotal study are comparable with the dropout rates observed with dopaminergics in first line therapy of less severely affected patients[1].

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.

Figure 1 Maintenance of effect – primary IRLS sum-score



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 QoL, respectively (Table 1);

[1] Oertel W et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol 2011; 10: 710-20.

Table 1 Maintenance of effect – secondary endpoints

Variable		Double-blind, 12-week study phase	Extension Phase
		Oxycodone/ naloxone PR (N=132)	Oxycodone/ naloxone PR (N=197)
CGI-1 score (severity of disease)	Base line	5.2 (0.9)	3.2 (1.6)
	End of study	3.0 (1.5)	2.5 (1.2)
RLS-6 daytime at rest (severity)	Base line	6.7 (2.2)	2.8 (2.9)
	End of study	2.5 (2.7)	1.4 (1.7)
RLS-QoL summary question 12	Base line	4.3 (0.9)	2.9 (1.6)
	End of study	2.9 (1.5)	2.1(1.1)
Sleep quantity MOS Sleep subscale, hours	Base line	5.2 (1.5)	6.1 (1.6)
	End of study	6.3 (1.3)	6.6 (1.2)
RLS pain score (NRS)	Base line	6.6 (2.5)	3.0 (2.8)
	End of study	2.7 (2.6)	1.6 (1.8)

2.2.2. Discussion

Although not yet fully understood the pathophysiology of RLS mainly concentrates on dopaminergic dysfunction, abnormalities in iron metabolism and in the central opioid systems[2,3]. There is also 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 [4, 5].

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.

Results 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 (single dose groups, pre-treatment including quantitative (number of treatments) and qualitative aspects (dopaminergic substances classes), gender and secondary endpoints).

As a considerable proportion of patients in the sought indication is expected to be older (≥ 65 years), and as 46% of patients included in study 3502 were ≥ 65 years, the respective subgroup analyses are considered rather meaningful. Consistently a clinically relevant treatment effect could be shown during

[2] Ondo WG. Restless legs syndrome: pathophysiology and treatment. Current treat options Neurol. 2014 Nov;16(11):317.
[3] Garcia-Borreguero D, Williams AM. An update on restless legs syndrome (Willis-Ekbom disease): clinical features, pathogenesis and treatment. Curr Opin Neurol. 2014 Aug;27(4):493-501.
[4] 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.
[5] 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 double-blind and the open label extension part of the pivotal study in older patients which was of a similar magnitude as compared to younger patients.

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.

The maintenance of treatment effect was investigated in the open extension phase of the pivotal study. The results clearly point to maintenance of efficacy. Although potential selection bias can occur in an open study, the MAH put in place different measures to minimise selection and attrition bias in the extension phase OXN3502S:

- Placebo patients were allowed to enter the extension phase;
- Subjects who discontinued prematurely due to loss of efficacy and who completed at least 8 weeks of double-blind phase were allowed to enter the extension phase;
- One week down titration prior to entering the extension phase not to carry over treatment effects from the double-blind phase;
- Subjects were still blinded about their double-blind phase treatment when entering the extension phase;
- Comparable proportions of patients from both treatment arms joined the extension phase (101/150 OXN PR; 96/154 Placebo);
- Almost all patients (97%) who completed the double-blind phase of study entered the extension phase;
- Eighty percent (80%) of subjects who entered the extension phase continued the study until the end. It is noted that similar or higher drop-out rates as compared to the pivotal study have been observed in studies with dopamine agonist approved as first-line therapy[6,7,8].

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 design however the CHMP considered that reasonable justifications for maintenance of effect up to 52 weeks of treatment were provided by the MAH.

The MAH stated that the dose range of OXN PR examined in the pivotal study was based on available knowledge from literature regarding opioid treatment in RLS, expert recommendations and experience from OXN PR in the treatment of pain. However, as a conservative approach the initial dose was chosen as 50% of the initial dose established for the treatment of pain in opioid naïve patients and of what was expected to be an effective dose. Results of the pivotal study with more than 70% of patients being up-titrated to doses higher than the initial dose, a majority of patients being treated within the dose range of 20-40 mg/day and a mean OXN PR dose of 22 mg/day (and comparable doses resulting from open extension study part) confirmed the adequacy of the evaluated dose range.

[6] Hening WA et al. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004; 27(3): 560-583.
[7] Trenkwalder C et al. The restless legs syndrome. The Lancet Neurol 2005; 4: 465-475.
[8] Trenkwalder C. et al. Treatment of restless legs syndrome: An evidence-based review and implications for clinical practice. Movement Disorders 2008b; 23(6): 2267-2302.

The CHMP considered that the results of the placebo-controlled study showed a robust and clinically relevant treatment effect of OXN PR.

2.3. Clinical safety

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

2.3.1. Results

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.

The most frequently reported adverse reactions for both studies OXN3502/S included constipation, nausea, fatigue, somnolence and hyperhidrosis. No difference was seen between both study phases with regard to nature of adverse reactions.

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. Furthermore, in view of daily dose groups from 10 mg to 60 mg OXN PR no significant differences in the safety profile were seen.

Augmentation

The review of adverse events of special interest showed that despite the careful evaluation of reports potentially indicating augmentation, the independent assessment did not reveal any case of augmentation throughout the entire study period of 52 weeks.

The CHMP noted that augmentation has been described for all investigated dopaminergic drugs[9] and that during the first year of treatment with dopaminergic agents, the frequencies of augmentation has been reported between 9 to 60% [10,11].

Opioid dependence

The review of the second identified adverse event of special interest '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.

No case of tolerance was reported during the double-blind and open-label extension part of study. The mean daily OXN PR dose remained stable during the course of the study and was even slightly lower during the open-label extension (18.12 mg) as compared to the double-blind part (22.62 mg). During

[9] Garcia-Borreguero D et al. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Medicines 2013; 14: 675- 68

[10] Vignatelli L. et al. EFNS guidelines on managment of restless legs syndrome and periodic limb movement disorder in sleep. Eur J Neurol 2006; 13: 1049-1065.

[11] Hogl B. et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. J Neurol 2010; 257: 230-237.

the course of the open extension study part, a very slight increase in main daily OXN PR dose was found however, this increase was accompanied by a further improvement in mean IRSL score.

No case of psychological dependence (addiction) was observed in the double-blind and open-label extension part of study even though a specific and profound assessment of 176 subjects using a specific questionnaire 4 weeks after the end of the extension phase has been performed.

Opioid abuse and misuse

No case of abuse or misuse was reported during the double-blind and open-label extension part of study.

The potential of OXN PR for abuse and related events in the RLS indication is expected to be comparable with that of the non-cancer pain indication, for which a positive benefit-risk ratio has been concluded. However, it is reassuring that the daily dose used in the RLS indication is clearly lower as compared to the pain indication (with respect to initial, average maintenance and maximum dose), that doses remained stable over time and that no case of tolerance or psychological dependence up to 52 weeks of treatment occurred.

Long term safety

For the assessment of the long-term safety of OXN PR in the treatment of RLS the experience with OXN PR from both clinical studies (OXN3502/S) and post marketing exposure in the treatment of pain has been taken into account due to the commonalities of the target populations with regard to demographic characteristics, medical history as well as concomitant medication.

The short- and long-term safety profile of OXN PR is established and well characterised in the pain indication (including non-cancer pain) due to an extensive study program with more than 4000 subjects as well as due to considerable post-marketing experience.

A thorough review of the safety data showed that the safety profile of OXN PR derived from the double-blind and open-label extension part of study is well in line with the known and well-established safety profile of OXN PR in the pain indication. It is also noted that the dosages required for the treatment of RLS are lower compared to dosages applied in the pain treatment [mean daily dose of 18.1 mg (OXN3502S) vs. 38.3 mg (OXN3001S) and 80.2 mg (OXN3006S)].

2.3.2. Discussion

Based on commonalities of RLS patients with non-cancer pain patients with respect to demographic characteristics, medical history as well as concomitant medication, a large overlap of the safety profile of OXN PR in both indications is to be expected and was further corroborated by a thorough review which demonstrated that the safety data derived from studies 3502/S were in line with the established safety profile of OXN PR in the pain indication regarding nature and severity of adverse events.

No case of augmentation, tolerance, psychological dependence (addiction), abuse or misuse was reported in the studies 3502/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. In addition, 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 and in the majority of these subjects no tapering had been performed.

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 abuse and misuse potential 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.

2.4. Risk management plan

The CHMP took note that a risk management plan will be put in place for Oxynal, Targin and associated names in order to characterise a possible risk of tolerance, dependence and drug abuse in long-term use in the IRLS.

2.5. Conclusions

In view of the data submitted, the CHMP considered that short term and long 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 and extension phase (OXN3502/S).

The CHMP concluded that, despite methodological limitations of the open label study design, reasonable justifications for maintenance of effect up to 52 weeks of treatment were provided by the MAH.

The CHMP also considered 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.

In addition, the CHMP highlighted the unmet medical need in the treatment of severe to very severe RLS after failure of dopaminergic treatment.

With regard to the general safety profile of OXN PR, the CHMP noted that the findings of the studies OXN3502/S are in line with the results of the post-marketing surveillance with OXN PR in the treatment of pain. No case of augmentation, tolerance, psychological dependence (addiction), abuse or misuse was reported in the studies OXN3502/S. Only few cases of withdrawal reaction and physical dependence were reported in the studies.

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.

The CHMP noted that 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.

2.6. Changes to the product information

The valid summary of product characteristics is the final version achieved during the Coordination group procedure with the amendments as mentioned in Annex III.

3. Benefit risk assessment and recommendation

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.

Appendix 1

Divergent positions to CHMP opinion

Article 13 of Regulation EC No. 1234/2008

Procedure No: EMEA/H/A-13/1402

Oxynal-Targin and associated names

Divergent statement

There are potential serious risks to public health related to the use of Oxynal/Targin in second line treatment of severe to very severe restless legs syndrome after failure of dopaminergic therapy. In general, due to its adverse events profile and dependence risk the use of strong opioids like oxycodone is preserved for conditions for the shortest period possible.

Although the short-term data do show an effect, the overall benefit-risk balance is negative. The sedative and other opioid related effects were frequent and serious, and are not considered to be outweighed by the potential benefits. Data of the open label extension study are not considered sufficient, as these do not provide an unbiased estimate of maintenance of efficacy, as it concerns a selected population. There are several uncertainties regarding long-term maintenance of effect, as tolerance usually occurs in opioids. Moreover, the pathogenic mechanism underlying RLS is still unclear and there is no conclusive evidence on the biological plausibility supporting the use of drugs acting on the opioid system in the management of RLS.

CHMP members expressing a divergent opinion:

Daniela Melchiorri (IT)	23 October 2014	Signature: ……...
Pierre Demolis (FR)	23 October 2014	Signature: ……...
Pieter de Graeff (NL)	23 October 2014	Signature: ……...