ANNEX II

Scientific conclusions and grounds for suspension / amendment of the summaries of product characteristics, package leaflets and labelling presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of modified-release oral opioid products in the level III of the WHO scale for the management of pain (intense sustained pain resistant to previous medications) (see Annex I)

1. Introduction

On 18 September 2009, the European Commission triggered a referral under Article 31 of Directive 2001/83/EC, as amended.

In the context of marketing authorisation procedures for oxycodone-containing products, possible differences in the safety profile of the originator and generic products had been raised concerning the interaction with alcohol. The CHMP was then asked by the European Commission to determine whether there is a need to take specific measures to deal with the consequences of the interaction between strong-opioid modified-release oral products and alcohol.

Therefore, the European Commission requested the CHMP to give its opinion on whether the marketing authorisations for authorised modified-release oral medicinal products of the WHO level III scale for the management of pain (intense sustained pain resistant to previous medications) (containing morphine, oxycodone, fentanyl and hydromorphone) should be maintained, varied, suspended or withdrawn.

Modified-release products are complex dosage forms designed to release drugs in a controlled manner to achieve desired efficacy and safety profiles. If, however, the modified-release system is influenced by an external factor or substance (such as alcohol), it is possible that a large quantity of the active substance is released in a short timeframe so that it resembles an immediate-release dosage form. This effect is known as 'dose-dumping'.

In order to assess the potential for dose-dumping of each product, MAHs of products in the level III of the WHO scale for the management of severe pain were asked to submit data on their products. Level III of the WHO scale includes fentanyl, hydromorphone, morphine and oxycodone, however no oral modified-release products containing fentanyl are currently authorised in the EU, as due to a marked first pass effect, oral administration of fentanyl is not feasible.

2. Quality issues

Dissolution data was submitted for two different controlled release systems of hydromorphone, four different controlled release systems of oxycodone, and seven different controlled release systems containing morphine.

From the products tested, fifty percent of the formulations were found to be affected by alcohol solutions *in vitro*. The effect of alcohol on the dissolution rate was mild in most cases, except for one morphine formulation (morphine once-daily capsules). This morphine formulation with polymethacrylate- triethylcitrate coating as modified-release mechanism has been identified as a product where dose dumping might occur when taken together with alcohol. The *in vitro* data showed a release of 80% of the drug within 15 minutes in 20% of alcohol solution. The polymethacrylate-triethylcitrate based formulation is highly sensitive to alcohol with its modified release properties being destroyed shortly after exposure, making it resemble an immediate release formulation.

A product containing hydromorphone and a prolonged release system consisting of ammonio methacrylate co-polymer type B (Eudragit RS) also suffered a significant effect of high concentrations of alcohol on *in vitro* dissolution. This product has never been marketed.

The remaining systems were not significantly affected by alcohol.

3. Clinical issues

For most of the products assessed, only *in vitro* data was submitted. In a limited number of cases, the MAH has also presented the results of *in vivo* studies and/or a review of adverse event reports which may have been related to the concomitant use of alcohol.

In vivo studies conducted with a hydromorphone formulation based on ammonio methacrylate co-polymer type B (Eudragit RS) confirmed the existing *in vitro* data suggesting that alcohol affects the formulation.

Another study conducted with a hydromorphone formulation based on cellulose acetate 398-10 and Macrogol 3350 formulation confirmed the conclusions of the *in vitro* studies that the effect of coadministered alcohol on PK parameters is rather limited.

The results of the only study with a morphine product (ethylcellulose N-50, methacrylic acid copolymer type C, polyethylene glycol 6000 and diethyl phthalate formulation) indicate that a relatively high quantity of alcohol has almost no effect *in vivo*.

A low number of cases of interaction between alcohol and opioid products have been reported, most reports involved intentional overdose or abuse in conjunction with other products and some were fatal. Given the type of products and patient population involved, it is acknowledged that underreporting is considerable.

Alcohol use is common in patients with chronic pain due to the fact that it reduces pain perception. In the scientific literature, drinking alcohol is referred as a coping mechanism to deal with the stress associated with pain.

This may be further aggravated by the fact that many patients with chronic pain will also suffer from depression. Concurrent depression and pain have a much greater impact than either disorder alone and, in patients with pain, depression is associated to more pain sites, greater pain intensity, longer duration of pain, and greater likelihood of poor treatment response (Bair, J et al., Psychosom Med. 2008 October; 70(8): 890-897).

The association between pain and drinking was evaluated by Brennan et al in a cohort of 401 elderly with different drinking behavior (Brennan, Addiction. 2005; 100(6): 777-86). Both problem drinkers and non-problem drinkers were included. Both problem drinkers as non-problem drinkers reported to use alcohol to manage pain, although in the latter group to less extent (see figure 1). Pain at baseline was a significant predictive factor for alcohol use in the 3-years follow-up period.

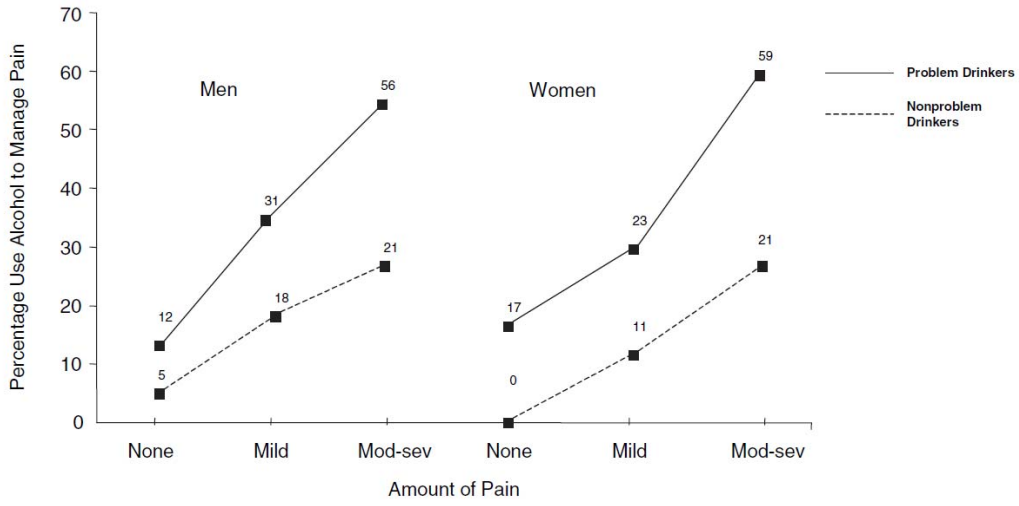

Figure 1 Use of alcohol to manage pain among problem and non-problem drinkers

Source; Brennan et al., Addiction 2005; 100 : 777-86

While it may be argued that patients may use less alcohol as a self-medication strategy if they are sufficiently treated with analgesics like opioids, the results of a recently published Danish Health survey (Ekholm et al. Eur J Pain 2009; 13: 606-12) reveal a different pattern of behavior. In this study, subjects were interviewed about their number of alcohol consumptions of the last week and frequency of binge drinking in the last month (5292 responders). About 20% of the responders reported chronic pain (>6 months). The association between chronic pain and alcohol use is summarized in the table below.

Table 2
Results from multivariate logistic regression analyses showing the association between chronic pain and alcohol behavior

	%	OR[a]	95% CI	*n*
High alcohol intake[b]				
Total	14.2			5159
Chronic pain and using opioids	10.8	0.71	0.39–1.31	119
Chronic pain and not using opioids	13.5	0.91	0.74–1.13	943
No chronic pain	14.4	1		4097
Binge drink at least once a month[c]				
Total	48.8			5186
Chronic pain and using opioids	22.3	0.36	0.22–0.57	120
Chronic pain and not using opioids	42.5	0.87	0.74–1.02	953
No chronic pain	50.9	1		4113
Consume alcohol less than once a month				
Total	17.1			5178
Chronic pain and using opioids	33.1	2.41	1.58–3.67	120
Chronic pain and not using opioids	21.9	1.44	1.19–1.73	951
No chronic pain	15.6	1		4107

[a] Adjusted for sex, age and combined school and vocational education.
[b] Weekly intake: men, >21 drinks; women, >14 drinks.
[c] Five drinks or more on one occassion.

Patients being treated with opioids tend to drink less alcohol than patients who do not use opioids at all. However, a significant percentage of the patients with chronic pain who uses opioids still reports high alcohol intake (10.8%) and binge drinking at least once a month (22.3%), despite existing warnings.

4. Benefit-Risk balance

Having considered all the data submitted, it can be concluded that the large majority of modified-release oral opioid products in the European Union do not exhibit a clinically significant interaction with alcohol.

While a pharmacodynamic interaction with alcohol may occur irrespective of the formulation, in most cases a pharmacokinetic interaction will not be clinically significant so as to warrant measures beyond the proposed wording for the product information. Fifty-percent of the formulations assessed are affected by alcohol solutions *in vitro*, but in most cases, the effect of alcohol on the dissolution rate is mild.

The exception is one morphine formulation using **polymethacrylate-triethylcitrate** coating as modified-release mechanism, for which dose dumping might occur when taken together with alcohol. The dissolution profile of this product (80% dissolved substance within 15 min in 20% alcohol) is beyond the limit of the Ph. Eur. for conventional-release products (NLT 75% dissolved active substance within 45 minutes). In addition, as the medicinal product based on this release-mechanism is intended for once a day dosing, the content of morphine is high and therefore the risk of adverse events following dose-dumping is also higher.

A significant effect was observed also in a hydromorphone once a day formulation which is not marketed in the EU.

In light of the existing data, including published data on the use of alcohol in patients treated with opioids, the Committee is of the opinion that the current warnings and contraindications are not sufficient to protect patients from the significant alcohol interaction observed with the polymethacrylate- triethylcitrate formulation. The Committee is also of the opinion that further minimisations measures would not adequately address the concern.

Therefore, patients taking this particular formulation are exposed to a significantly greater risk of developing serious adverse reactions such as respiratory depression and death.

For all other strong-opioid modified release oral products in the European market (formulations not containing polymethacrylate-triethylcitrate), no significant risk of dose-dumping due to alcohol use was identified. However, for all of these products, a pharmacodynamic interaction may occur and should be mentioned in the Product information of all products in a consistent manner. While most products already contain warnings and references to this interaction in the SPC, the wording should be harmonised to ensure the same level of awareness.

The assessment within this procedure provided an overview of the modified-release systems used in the European Union in oral opioid products. Not all MAHs of modified-release oral opioid products in the level III of the WHO scale for the management of pain in the European market submitted data, and so it can not be guaranteed that all products approved in the EU have been assessed. The National Competent Authorities should therefore determine, based on the modified-release mechanism of the products approved in their Member State, the appropriate actions to be taken for individual products.

5. Re-examination procedure

Following the CHMP Opinion of 22 July 2010, one MAH submitted detailed grounds for the re-examination of the opinion.

The MAH expressed the view that:

1. The CHMP had not addressed the issue of the additional risk to patients posed by modified release formulations of opioids which exhibit a greater vulnerability to alcohol compared with the reference product, whilst conferring no additional patient benefit.

2. The Opinion did not take account of the earlier advice of its own working parties, namely the EWP and QWP, which had been requested by the CMD(h); nor did it provide any proper reasons for discounting that advice.

3. The CHMP's conclusions were arbitrary. Firstly, the Opinion does not provide any information regarding the acceptance criteria to be applied in relation to the clinical significance of pharmacokinetic interactions with alcohol. Secondly, the CHMP's approach to alcohol interaction is inconsistent with its approach to food interactions.

4. The Opinion was not properly reasoned. In particular, assumptions were made about the behaviour of some formulations based solely on the excipients; in this respect the CHMP did not take into account the evidence provided in the Oral Hearing on 23 June 2010 that such assumptions are flawed.

Further to the request from the MAH, the CHMP convened an Ad-Hoc Expert meeting including experts on technology/formulation science, pharmacokinetics and clinical/medical practice in order to deliver answers on a consultative basis to specific questions in relation to the grounds for re-examination.

Having assessed the detailed grounds for re-examination provided by the MAH, the rapporteurs assessment reports, the conclusions from the ad hoc expert meeting together with the MAH's expressed concerns on the conclusions of the ad hoc expert meeting and all the information submitted during the referral procedure, the CHMP discussed each one of the grounds submitted:

1. The CHMP had not addressed the issue of the additional risk to patients posed by modified release formulations of opioids which exhibit a greater vulnerability to alcohol compared with the reference product, whilst conferring no additional patient benefit.

The issue of additional risk to patients was addressed by CHMP in its initial opinion, and as a consequence a recommendation was adopted to suspend and reformulate the formulations where the interaction was of such magnitude that the products essentially resemble an immediate release formulation (while containing the opioid dose appropriate for a modified release formulation). In this context, the fact that the product is meant for use once or twice a day may be of importance given the higher dose usually contained in once a day formulations.

In addition, the CHMP agreed on the inclusion for all other products in the European market of a pharmacodynamic warning. This is justified on the basis that a pharmacodynamic interaction between opioid products and alcohol may occur irrespective of the formulation. The Committee also discussed the possibility of the introduction of a pharmacokinetic warning in those cases where some degree of additional formulation interaction could be suspected. In this respect, it was noted that the *in vitro - in vivo* correlation is unclear in most cases, and therefore it would be inappropriate to assume a pharmacokinetic interaction. This is clearly demonstrated by the existing data for one specific product for which the in vitro interaction is significant but where the pharmacokinetic parameters did not differ significantly among subjects taking the product with water or with alcohol (ethylcellulose N-50, methacrylic acid copolymer type C, polyethylene glycol 6000 and diethyl phthalate product).

The Committee also reflected on the usefulness for prescribers and patients of a pharmacokinetic warning in the Product Information referring to the *in vitro* data. Considering that the proposed pharmacodynamic warning already advises against concomitant use with alcohol, considering also the limitations of the *in vitro* data and difficulties in its interpretation by prescribers, the majority of the Committee was of the opinion that the addition of a pharmacokinetic interaction warning based on a description of the *in vitro* data would not favour the clarity of the message to patients and prescribers regarding the need to avoid concomitant use with alcohol.

2. The Opinion did not take account of the earlier advice of its own working parties, namely the EWP and QWP, which had been requested by the CMD(h); nor did it provide any proper reasons for discounting that advice.

When adopting its 22 July 2010 opinion on this procedure, CHMP was fully aware of the positions of the different working parties. The advice of the QWP was that formulations should, if possible, be developed such that a physicochemical incompatibility with alcohol is avoided. Where not possible, the QWP recommended the inclusion of differential wording in the Product Information. The question of what could be considered as a clinical significant interaction with alcohol was left for the EWP to consider. The advice of the EWP was to consider the worst case scenario, including gastric residence times of 1-2 to hours and potential exposure to high concentrations of alcohol. As a consequence, where accelerated drug release is seen, the EWP's recommendation was for label warnings and risk management strategies to be considered.

In its detailed grounds for re-examination the MAH referred to statistical analysis confirming different behaviours in the presence of alcohol for a generic and its originator product. This aspect is outside the scope of this procedure and it does not provide any relevant information to the issue at stake. More than confirming that the generic and originator are bioequivalent, in this review it is important to consider whether the observed in vitro effect constitutes an unacceptable risk for patients.

In its assessment, the Committee took into consideration data submitted for the different timepoints. An important interaction following alcohol consumption becomes progressively less likely with time due to dilution effect by gastric secretions and saliva, and gastric emptying. This is demonstrated by measurements of gastric-duodenal ethanol levels after consumption of alcohol in healthy volunteers. Gastric ethanol concentrations dropped rapidly after the consumption of alcohol by 70% in 10 min (Levitt et all, Am J Physiol Gastrointest Liver Physiol 273:951-957, 1997). With food the gastric emptying of alcohol is delayed, but still significant (50-60% in 1 hour, Levitt, 1997, and Cortot et al, Digestive Diseases and Sciences 1986; 31:343-48).

3. The CHMP's conclusions were arbitrary. Firstly, the Opinion does not provide any information regarding the acceptance criteria to be applied in relation to the clinical significance of pharmacokinetic interactions with alcohol. Secondly, the CHMP's approach to alcohol interaction is inconsistent with its approach to food interactions.

The Opinion does not provide information on the acceptance criteria to be applied in relation to the clinical significance of pharmacokinetic interactions because there are currently no standard acceptance criteria to be applied in this context.

Further to that, the IVIV correlation is, at present time, uncertain for most products. It follows from the above that data presented on the *in vitro* effects of alcohol on the dissolution profile of these products are not necessarily a reliable predictor of *in vivo* behaviour and therefore recommendations such as suspension and reformulation of products should only be adopted for products for which the in vitro interaction is of such magnitude that the products are considered to pose serious risks to the patients.

In its detailed grounds for re-examination, the MAH referred to a competitor product in which the release of oxycodone is accelerated in the presence of alcohol as an example of a potentially clinically meaningful interaction. According to the data on a competitor product presented by the MAH requesting re-examination, this product starts to exhibit accelerated release of the active substance after approximately 30 min of exposition to alcohol, and is claimed to release 76.5% of the oxycodone dose within one hour of exposure to concentrations of alcohol around 24%. A product with this dissolution profile cannot be considered to behave as an immediate release formulation.

A similar dissolution study from 2007 however, showed that at 60 minutes the dissolution rate of the reference product (considered by the MAH to be a safe product) in the absence of alcohol was actually higher that the dissolution rate of the competing product presented when exposed to 20% alcohol.

It is of note that, in the data presented by the MAH for this competitor product, the most pronounced effect of alcohol is not at the highest alcohol concentrations tested (40%), but between 28%-32%. This further illustrates the limitations of the data presented.

From all the above mentioned considerations, including the limitations of the existing data and the current status of scientific knowledge, it follows that general recommendations for acceptance criteria to be applied in relation to the clinical significance of pharmacokinetic interactions with alcohol can not be determined by the Committee at this time.

The MAH further considered, in its grounds for re-examination, that the CHMP opinion was inconsistent in its approach regarding alcohol versus food interactions.

It is well known that food can have an effect on the pharmacokinetic parameters of medicinal products. It is important to note in this regard that the effects of food related interactions are measured in vivo, and therefore the data on food effect reflects, as accurately as possible, the real extent of the interaction. Food related interactions are taken into consideration and reflected in the SPC and package leaflet for the benefit of patients and prescribers.

For alcohol, the majority of the data available relates to *in vitro* testing only, and therefore cannot be assumed, for the reasons previously explained, to be directly reproduced *in vivo*. Considering that the proposed pharmacodynamic warning already advises against concomitant use with alcohol, considering also the limitations of the *in vitro* data and difficulties in its interpretation by prescribers, the majority of the Committee was of the opinion that the addition of a pharmacokinetic interaction warning based on a description of the *in vitro* data would not favour the clarity of the message to patients and prescribers regarding the need to avoid concomitant use with alcohol.

It is therefore concluded that the approach is not inconsistent, firstly because in the case of alcohol, a recommendation not to take the product with alcohol will always exist regardless of the formulation. Secondly, because unlike alcohol, SPC information on food interactions will reflect in vivo studies and therefore have clear added value for the prescriber and the patient.

4. The Opinion was not properly reasoned. In particular, assumptions were made about the behaviour of some formulations based solely on the excipients; in this respect the CHMP did not take into account the evidence provided in the Oral Hearing on 23 June 2010 that such assumptions are flawed.

The anticipated increase in dissolution rate observed for modified-release products is a result of the modified release system being rendered unstable in the presence of alcohol. This will be related to the specificities of each formulation, namely the physical characteristics of the excipients and the manufacturing process. It is however clear that, in the cases where the highest degree of in vitro interaction was observed, the high alcohol solubility of the excipients provided a clear explanation for the observation.

The MAH mentioned in his grounds for re-examination a paper by Smith at al (In vitro dissolution of oral modified-release tablets and capsules in ethanolic media, International Journal of Pharmaceutics 398 (2010) 93-96) to illustrate that formulations should not be assumed to be unaffected by alcohol without data being evaluated.

In its initial Opinion, the CHMP did not conclude that the formulations analysed were unaffected by alcohol. It is clearly stated in the Opinion that 50% of the formulations were found to be affected by alcohol in vitro. The question under discussion is, however, whether the magnitude of the interaction is such that it can be assumed to have clinical significance and represent a significant risk for the patient.

It should be noted that, while the authors of the above mentioned paper go on to conclude that '*in vitro dissolution may provide evidence regarding the ruggedness of formulations to ingested alcohol*', no recommendations are issued to specific products given that '*…further research is needed to understand the relationship between dosage form, product formulation and configuration and drug release in the presence of ethanol.'*

The CHMP having assessed all the detailed grounds for re-examination and argumentation presented by the MAH and having considered the views of the Rapporteurs, the scientific discussion within the Committee and the conclusions of the ad hoc expert group as well as the concerns raised by the MAH in this respect, concluded that products with a polymethacrylate-triethylcitrate coating are harmful under the normal conditions of use and that, for the remaining products, the Product Information should be amended to include a warning and recommendation for avoiding concomitant use with alcohol. The Committee is therefore of the opinion that its 22 July 2010 opinion should be maintained.

Grounds for amendment of the summaries of product characteristics, package leaflets and labelling

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC, as amended for modified-release oral opioid products in the level III of the WHO scale for the management of pain (intense sustained pain resistant to previous medications) on the EU market,
- The Committee considered all the available data submitted by the MAHs,
- The Committee considered that a pharmacodynamic interaction between opioid products and alcohol may occur irrespective of the formulation,
- The Committee considered that, based on the published literature, a significant percentage of the patient population using these products does not abstain from alcohol consumption despite the existing warnings and contraindications,
- The Committee considered that products without a polymethacrylate-triethylcitrate coating as modified-release mechanism do not suggest a significant interaction with alcohol considered to be harmful under normal conditions of use,
- The Committee considered, however, that as a pharmacodynamic interaction with alcohol may occur, the product information of the above mentioned products should describe in a clear and harmonised manner the pharmacodynamic interaction between opioid products and alcohol,

The Committee therefore recommended the amendment of the Marketing Authorisation for which the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III.

As not all medicinal products concerned by this review submitted data, the National Competent Authorities should ensure, based on the modified-release mechanism of the products approved in each Member State, that the appropriate actions are taken for individual products.

Grounds for suspension of the marketing authorisation

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC, as amended for modified-release oral opioid products in the level III of the WHO scale for the management of pain (intense sustained pain resistant to previous medications),
- The Committee considered all the available data submitted by the MAHs,
- The Committee noted that a pharmacodynamic interaction between opioid products and alcohol may occur irrespective of the formulation,
- In addition, the Committee considered that the dissolution profile of products containing a polymethacrylate-triethylcitrate coating as modified-release mechanism is significantly affected in the presence of alcohol, leading to an uncontrolled rapid release of the majority of the active substance, and therefore the product exhibits a significant interaction with alcohol with potentially significant clinical effects (e.g. respiratory depression and death),
- The Committee, based on the published literature, considered that a significant percentage of the patient population using these products does not abstain from alcohol consumption despite the existing warnings and contraindications, and that therefore the existing risk minimisation measures do not adequately address the concern,
- The Committee is also of the opinion that further risk minimisation measures would not adequately address the concern,
- The Committee therefore considered that patients exposed to the above mentioned products and concomitant intake of alcohol are at significantly greater risk of developing serious adverse reactions such as respiratory depression and death,
- The Committee took the view that modified-release oral opioid products in the level III of the WHO scale for the management of pain containing a polymethacrylate-triethylcitrate coating as modified-release mechanism are harmful under the normal conditions of use in accordance with article 116 of Directive 2001/83/EC, as amended.

Consequently, the CHMP has recommended the suspension of the marketing authorisation for modified-release oral opioid products in the level III of the WHO scale for the management of pain containing a polymethacrylate-triethylcitrate coating as modified-release mechanism (see annex I).

For the suspension to be lifted, the Marketing Authorisation Holders need to provide evidence that the product has been reformulated, that it exhibits an acceptable release profile with the same quality, safety and efficacy profile of the currently authorised formulation but without the clinically significant interaction with alcohol. The new formulation must be approved by the National Competent Authorities of the concerned Member States (see Annex IV).