ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR NON-RENEWAL OF THE MARKETING AUTHORISATION

Scientific conclusions

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

1. Introduction

Ethypharm submitted an application for the renewal, under the mutual recognition procedure, of Ethirfin and associated names, 20mg, 60 mg, 120 mg and 200 mg.

The application was submitted to the reference Member State Denmark and to the concerned Member States (CMS) Germany, Ireland, Italy and the United Kingdom.

During the assessment, major issues on safety were raised by Germany and the United Kingdom, hence the procedure was referred to CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended.

At the end of the CMD(h) procedure, and since there could be no agreement the procedure was referred to the CHMP.

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by Denmark on 30 October 2009. Germany and the United Kingdom raised potential serious risk to public health concerns due to the dissolution profile of the modified-release product allowing the release of up to 80% of the active substance within 30 minutes, when exposed to 20% alcohol.

The CHMP considered the matter and adopted an Opinion in July 2010 recommending the renewal of the marketing authorisation subject to conditions considered essential to the safe and effective use of the product. Following a request from the European Commission, in September 2010 the CHMP further considered, in light of the benefit-risk balance and the requirements of article 24(2) of Directive 2001/83/EC as amended, the recommendation previously adopted for the product.

2. Quality aspects

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’.

The prolonged release properties of this product are ensured by the film coating composed of the polymethacrylate derivative plasticized by triethylcitrate (TEC) to which talc and hydrophobic colloidal silica are added.

The polymethacrylate is a polymer that forms a continuous film when processed. This film acts as a membrane allowing the diffusion of the active substance depending on its permeability. The polymethacrylate preparation is miscible in water and in ethanol.

The triethylcitrate acts as a plasticizer. Triethylcitrate is water-soluble and miscible in ethanol.

Dissolution profiles have been performed using the 200 mg capsule strength only. This strength is considered representative for the other (20, 60 and 120 mg) strengths as all strengths are dose proportional and manufactured with the same microgranules. The dissolution test method used was the routine test, i.e. paddle apparatus at 100 rpm with 1000 ml of medium. The dissolution medium was water, loaded with 5, 10 and 20% ethanol in line with the EMA QWP Q&A document Need for in

vitro Dissolution Studies with Alcohol for Modified Release Oral Products Including Opioid Drug Products. Dissolution was evaluated over an 8-hour period. It was shown that the dissolution rate increases with increased concentration of ethanol in the dissolution medium. Out of specification results were obtained after 0.25 hours in 20% alcohol, after 0.5 hour in 10% alcohol and after 2 hours in 5% alcohol.

The results of the dissolution tests demonstrate that the formulation is within the limit of the Ph.Eur. for conventional-release products (NLT 75% dissolved active substance within 45 minutes) and therefore experiences severe alteration, leading to an uncontrolled rapid release of the majority of the active substance.

3. Clinical aspects

No *in vivo* studies have been performed to investigate the effect of alcohol on the absorption of the product.

No adverse events have been reported for Ethirfin and associated names suspect to be related to the concomitant use of alcohol.

It is noted that the product already contains a specific contraindication for concomitant intake of alcohol. However, 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). The amount of pain at baseline was a significant predictive factor for alcohol use in the 3-years follow-up period.

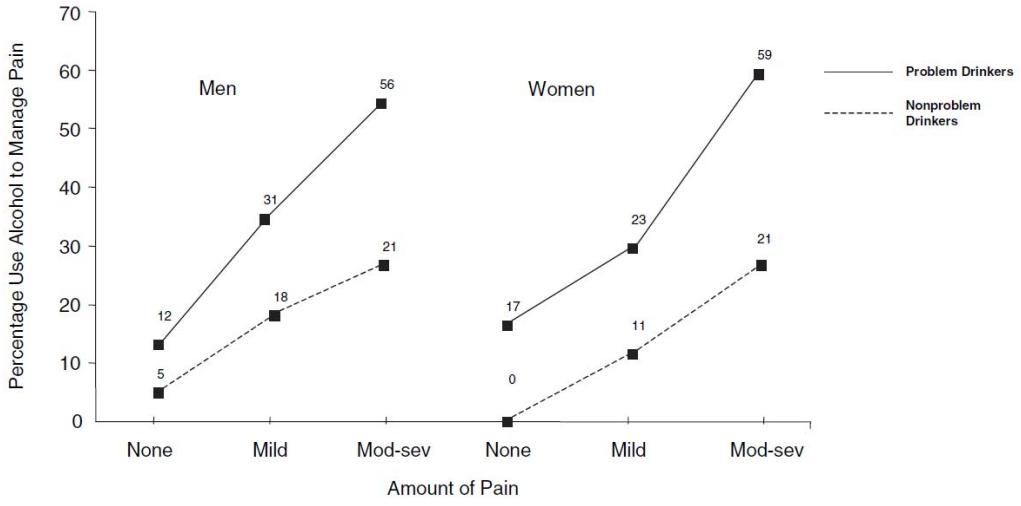

Figure 1 Use of alcohol to manage pain among problem and non-problem drinkers

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 assessment

Having considered the overall submitted data provided by the MAH, the CHMP concluded that

- A pharmacodynamic interaction between opioid products and alcohol may occur irrespective of the formulation,
- In addition, the dissolution profile of Ethirfin 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),
- 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, 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

The CHMP therefore recommended the non-renewal of the marketing authorisation in line with article 24(2) of Directive 2001/83/EC as amended.

Grounds for non-renewal of the marketing authorisation

Whereas

- The Committee considered the procedure under Article 29(4) of Directive 2001/83/EC, as amended for Ethirfin and associated names,
- The Committee considered all the data submitted by the MAH,
- The Committee noted that a pharmacodynamic interaction between opioid products and alcohol may occur irrespective of the formulation,
- The Committee considered that the dissolution profile of Ethirfin and associated names is significantly affected in the presence of alcohol, leading to an uncontrolled rapid release of the majority of the active substance, 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, and took the view that the risk-benefit balance of the product is not positive under normal conditions of use.

the CHMP, therefore recommended the non-renewal of the marketing authorisation in line with article 24(2) of Directive 2001/83/EC as amended.