ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 25 Mikrogramm/h Transdermales Pflaster	25 µg/h	transdermal patch	transdermal route
Austria		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 50 Mikrogramm/h Transdermales Pflaster	50 µg/h	transdermal patch	transdermal route
Austria		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 75 Mikrogramm/h Transdermales Pflaster	75 µg/h	transdermal patch	transdermal route
Austria		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 100 Mikrogramm/h Transdermales Pflaster	100 µg/h	transdermal patch	transdermal route
Belgium		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm Pharmaceuticals 25µg/h Pleister voor transdermaal gebruik/Dispositif transdermique/transdermales Pflaster	25 µg/h	transdermal patch	transdermal route
Belgium		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm Pharmaceuticals 50µg/h Pleister voor transdermaal gebruik/Dispositif transdermique/transdermales Pflaster	50 µg/h	transdermal patch	transdermal route
Belgium		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm Pharmaceuticals 75µg/h Pleister voor transdermaal gebruik/Dispositif transdermique/transdermales Pflaster	75 µg/h	transdermal patch	transdermal route
Belgium		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg	Fentanyl Helm Pharmaceuticals 100µg/h Pleister voor transdermaal gebruik/Dispositif	100 µg/h	transdermal patch	transdermal use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
		Germany	transdermique/transdermales Pflaster			
Germany		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 25 µ/h Transdermales Pflaster	25 µg/h	transdermal patch	transdermal use
Germany		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 50 µ/h Transdermales Pflaster	50 µg/h	transdermal patch	transdermal use
Germany		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 75 µ/h Transdermales Pflaster	75 µg/h	transdermal patch	transdermal use
Germany		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 100 µ/h Transdermales Pflaster	100 µg/h	transdermal patch	transdermal use
Italy		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 25 µg/h cerotto transdermico	25 µg/h	transdermal patch	transdermal use
Italy		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 50 µg/h cerotto transdermico	50 µg/h	transdermal patch	transdermal use
Italy		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanyl Helm 75 µg/h cerotto transdermico	75 µg/h	transdermal patch	transdermal use
Italy		Helm Pharmaceuticals GmbH	Fentanyl Helm 100 µg/h cerotto	100 µg/h	transdermal patch	transdermal use

Member State EU/EEA	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration
		Nordkanalstrasse 28 20097 Hamburg Germany	transdermico			
Netherlands		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 25 µg/h Pleister voor transderaal gebruik	25 µg/h	transdermal patch	transdermal use
Netherlands		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 50 µg/h Pleister voor transderaal gebruik	50 µg/h	transdermal patch	transdermal use
Netherlands		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 75 µg/h Pleister voor transderaal gebruik	75 µg/h	transdermal patch	transdermal use
Netherlands		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentrix 100 µg/h Pleister voor transderaal gebruik	100 µg/h	transdermal patch	transdermal use
Portugal		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanilo Helm	25 µg/h	transdermal patch	transdermal use
Portugal		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanilo Helm	50 µg/h	transdermal patch	transdermal use
Portugal		Helm Pharmaceuticals GmbH Nordkanalstrasse 28	Fentanilo Helm	75 µg/h	transdermal patch	transdermal use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
		20097 Hamburg Germany				
Portugal		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanilo Helm	100 µg/h	transdermal patch	transdermal use
Slovenia		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanil HELM 25 mikrogramov/h transdermalni obliži	25 µg/h	transdermal patch	transdermal use
Slovenia		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanil HELM 50 mikrogramov/h transdermalni obliži	50 µg/h	transdermal patch	transdermal use
Slovenia		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanil HELM 75 mikrogramov/h transdermalni obliži	75 µg/h	transdermal patch	transdermal use
Slovenia		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanil HELM 100 mikrogramov/h transdermalni obliži	100 µg/h	transdermal patch	transdermal use
Spain		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanilo Matrix Helm 25 microgramos/hora parches transdérmicos EFG	25 µg/h	transdermal patch	transdermal use
Spain		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanilo Matrix Helm 50 microgramos/hora parches transdérmicos EFG	50 µg/h	transdermal patch	transdermal use
Spain		Helm Pharmaceuticals GmbH	Fentanilo Matrix Helm 75	75 µg/h	transdermal patch	transdermal use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
		Nordkanalstrasse 28 20097 Hamburg Germany	microgramos/hora parches transdérmicos EFG			
Spain		Helm Pharmaceuticals GmbH Nordkanalstrasse 28 20097 Hamburg Germany	Fentanilo Matrix Helm 100 microgramos/hora parches transdérmicos EFG	100 µg/h	transdermal patch	transdermal use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF FENTRIX AND ASSOCIATED NAMES (SEE ANNEX I)

Fentanyl is a synthetic opioid analgesic, belonging to the piperidine derivatives, and is chemically related to pethidine. Fentanyl is 75-100 times more potent than parenteral morphine. The analgesic and sedative action of fentanyl is proposed to be mediated mainly through μ-opioid-receptors. Fentanyl has been marketed as iv anaesthetic since the 1960s. Today fentanyl is extensively used as an anaesthetic and analgesic. Fentanyl has a high lipid solubility which makes it suitable for transdermal administration.

The transdermal fentanyl patch technology has been used clinically to provide analgesia since 1991. Transdermal patches are applied to intact skin in order to deliver at a constant rate the active substance to the systemic circulation. Once the patch is applied to the skin the drug diffuses in the subcutaneous tissues and forms a reservoir. Therefore, the elimination half-life is longer compared to other administration routes, with about 17 h for fentanyl after transdermal administration, compared to parenteral and transmucosal administered drug of 7 h. The release of the drug from the patch is controlled without membrane. The rate controlling step of drug absorption is commonly the permeation through the skin.

The legal basis for this application refers to: Article 10(1) of Directive 2001/83/EC, as amended. The reference medicinal product is Dorogesic 25 - 100 μg/h, (MAH Janssen-Cilag, Neuss, Germany).

However, the objecting Concerned Member State (CMS) considered that the authorisation of this medicinal product Fentrix, transdermal patch, may present a potential serious risk to public health on the grounds of non-clinical and clinical safety. The issue was referred to the CMD(h) and an assessment was carried out by the Reference Member State (RMS). Because no agreement was reached at Day 60, the procedure was referred to the CHMP. The CHMP assessed the dossier and the available data, including the issues raised by the objecting CMS.

- Non-clinical issues

The Applicant acknowledged that only non-clinical single dose studies have been performed in spite of the fact that section 4.2 “Dermal tolerance testing” of the Note for Guidance on Non-clinical Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00), indicates that dermal tolerance is tested by a single and repeat dose administration and an evaluation of the sensitising potential. The Applicant’s justification was that the evaluation of the local tolerance after repeat dose administration has been carried out during the multiple dose bioequivalence study in humans.

However it was the view of the objecting Member States (MS) that the excipients in this application are qualitatively different to those of the reference product and that the Applicant had used the monolayer instead of the bilayer version of the patch in some non-clinical investigations. It was therefore argued that specific dermal irritation studies are required according to the guidelines mentioned above.

In order to assess the applicability of this objection, the CHMP took into account that the subsequent points:

The current bilayer patch differs from the earlier monolayer formulation only by the additional insertion of a reservoir layer. This reservoir was introduced between the layer exposed to the skin (donor layer) and the backing film. Nevertheless, the crucial donor layer has the identical composition in both monolayer and bilayer patches. For this reason, it was argued that the non-clinical studies testing the monolayer version should also be accounted for when the local tolerability is assessed.

The dermal tolerability of the current bilayer patch formulation was non-clinically analysed in comparison to the reference product “Dorogesic 25” in rabbits as part of the pharmacokinetic studies A/PK 02-P012 and A/PK 02-P013. In Study A/PK 02-P013, skin reactions were assessed in

compliance with existing guidance on single dermal tolerance tests (CPMP/SWP/2145/00) and were rated negligible to slightly irritant for both test item and reference patch. These findings have been corroborated by a comparable tolerability profile determined in clinical studies (see below).

In principle, the non-clinical data on local tolerance of the bilayer patch should have been complemented by an analysis of its sensitisation potential. However, the predominant constituents of the patch - mainly two of the adhesives, were not found to be sensitive to the skin of guinea pigs when tested alone according to guidelines CPMP/SWP/2145/00 and OECD 406 (Buehler method). As absence of any sensitising potential is also well-known for the active substance and all other excipients of the patch and could be clinically confirmed (see below), no new information can be reasonably expected from additional studies in animals.

The guideline on non-clinical investigations of local tolerance was developed before the introduction of transdermal systems. Consequently, the requirements set in these regulations have been taken rather as recommendations by European Member States and applicants in the past than absolute requirements.

Taking all these aspects into consideration, the CHMP accepted the argument that the available non-clinical data sufficiently demonstrate the comparable local tolerability of Fentrix and Dorogesic. For this reason, it was considered reliable to assume that further investigations would not substantially add to this favourable safety profile and should hence be avoided for reasons of animal welfare as has been common practice in other European procedures in the past.

- Clinical issues

Local tolerance
The Applicant acknowledged that only non-clinical single dose studies have been performed. The justification for this was that the evaluation of the local tolerance after repeat dose administration had been carried out during the multiple dose bioequivalence study in humans.

The RMS considered it to be reasonable and ethical to assess skin tolerability of opioid containing transdermal patches as part of comparative bioavailability studies. This approach has generally been accepted and supported by other EU and non-EU authorities as well.

The objecting MS argued that although this study was neither designed nor powered to assess the tolerability profile, its results suggest a worse safety profile for the test product.

As there is currently no explicit EU guidance available on the evaluation of local tolerability of transdermal systems, and considering previous experience with marketing authorisations of several other transdermal patches in the EU, the CHMP noted that skin tolerability had always been assessed as part of the pharmacokinetic studies. Both clinical pharmacokinetic studies, single dose (SD) as well as multiple dose (MD), confirmed that the Fentrix patch is in general well tolerated when applied to the human skin.

Local irritation potential
Initially, the Applicant submitted the data comparing the adverse events without any statistical analysis and a statistical comparison was requested. The McNemar test was then used investigating whether significant differences between the test and the reference in the number of patients who suffered adverse events were observed or not. This test does not take into account the temporal evolution of events - only if the subject suffered adverse events with the test, or with reference, or with both, or with none.

The objecting MS were of the view that the study results needed to be reanalysed because initially the irritation data had not been appropriately assessed. It was therefore argued that this could not be used as supportive of a similar safety profile as required by the guideline. On the contrary, the visual inspection of the data was suggestive of a worse skin irritation potential.

Single dose study: the mean score for test was 0.39 and 0.25 for the reference.
Multiple dose study: the number of observations with skin irritation above score 1 was 77 for the test and 56 for the reference, in the same number (26) of subjects with skin irritation.

Therefore, the objecting CMS performed a new statistical analysis based on a logistic regression mixed model where the likelihood of having an AE depended both on the number of observations and treatments (fixed effects) and subject (as a random effect). Skin reactions with a score 1 were not included in the analysis because these are very mild and could be found in any transdermal product in the market. Performing this model, statistically significant differences were found between treatments in both studies (the single dose study and the multiple dose study), and the point estimate of the odds ratio was 8.35 in the single dose study and 1.45 in the multiple dose study. Therefore, the objecting MS were of the view that the difference was not only statistically significant but that the difference was also considered to be clinically relevant.

Following the approach of Kuss (Kuss O: How to use SAS for logistic regression with correlated data. SAS User Group International (SUGI) Conference Proceedings 27, Paper 261-27 (2002)), the Applicant recalculated the logistic mixed model using the SAS Procedure NLMIXED (SAS Version 9.1.3). Choosing the binary endpoint ("skin reaction > 1") included treatment (test vs. reference) and observation (in h from first administration) as fixed explanatory variables and a random subject effect. The results the Applicant obtained for the treatment effect using this model are as follows:

Single dose: OR estimate: 5.67, 95 % CI [1.12; 28.78] p = 0.0371
Multiple dose: OR estimate: 1.41, 95 % CI [0.97; 2.05] p = 0.0716

The OR estimates are close to the ones reported by the objecting CMS, although not exactly identical. This can be possibly attributed to different algorithms/specifications of the model or similar reasons. More importantly, the Applicant reproduced the statistically significant product effect for the single dose study (p= 0.0371), whereas for the multiple dose study the differences were not statistically significant (p=0.0716).

To clarify the clinical relevance of these concerns and to assess the significance of the statistical analysis performed by the CMS, the following points were considered by the CHMP:

- Each of the clinical pharmacokinetic studies (single dose (SD) as well as multiple dose (MD)), confirmed that for the Fentrix patch, the percentage of skin irritation scores of 0 (no irritation) and score 1 (minimal erythema, barely perceptible, scoring according to the FDA Guidance for industry, *Skin Irritation and Sensitization Testing of Generic Transdermal Products)* reached more than 90 %. From experience, these values were considered to be well in line with the results of other fentanyl generic patches.

- In the statistical analysis performed by the objecting CMS, only a small percentage of incidences of skin irritations, calculated as 3.28 % (SD)/8.46%(MD) for the Fentrix patch and 0.64 % (SD)/5.93%(MD) for the reference patch, have been included to evaluate the comparability of the safety profile. If it can be agreed that irritation scores at or below 1 are without clinical relevance and that more than 90 % of the reported incidences are well within this accepted range, it would consequently be erroneous to base the decision about a potential serious risk solely on a small portion (less than 4 % (SD) respectively 9 % (MD)) of the entity.

It is an accepted clinical reality that for transdermal therapy a skin irritation score of 1 is common and without further clinical relevance. Due to the mechanical stressing during the detachment of the adhesive layer from the upper skin area, irritation is unavoidable; therefore slight skin irritation is always induced by the repetitive use of transdermal patches. Based on the bioequivalence studies, Fentrix patches have confirmed comparability to the reference medicinal product, Dorogesic SMAT. This proves that even the visually inspected, slightly increased incidence of skin irritations obviously has no further influence on the permeability of the drug substance, if compared to the reference

medicinal product. Hence, efficacy and systemic tolerability of the active substance remains unaffected.

GROUNDS FOR POSITIVE OPINION

Whereas

- it was considered to be reasonable and ethical to assess skin tolerability of opioid containing transdermal patches as part of comparative bioavailability studies

- the Fentrix transdermal patch was shown to be well tolerated and comparable to the reference medicinal product Dorogesic

the CHMP has recommended the granting of the Marketing Authorisation for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Fentrix and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.