ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS AND MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Belgium		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Cyprus		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl[1]	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

[1] Name approval pending

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Czech Republic		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Denmark		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Estonia		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Finland		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl[2]	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

[2] Name approval pending

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Germany		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Greece		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Hungary		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Iceland		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Ireland		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Italy		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl[3]	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Latvia		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

[3] Name approval pending

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Lithuania		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Luxembourg		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Norway		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Poland		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Slovak Republic		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Slovenia		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
Spain		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl[4]	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

[4] Name approval pending

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK		Abstral	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use
United Kingdom		ProStrakan Ltd, Galabank Business Park, Galashiels TD1 1QH UK	Rapinyl	50µg 100µg 200µg 300µg 400µg 600µg 800µg	Sublingual tablet	Sublingual use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF RAPINYL AND ASSOCIATED NAMES (see Annex I)

A marketing authorization application was submitted by the Applicant ProStrakan Ltd through the Decentralised Procedure for Rapinyl, a sublingual tablet containing 50, 100, 200, 300, 400, 600 or 800 µg fentanyl, as citrate. Fentanyl is a well-known and widely used synthetic short acting strong opioid analgesic, used in the treatment of patients with severe pain. Rapinyl is intended for the treatment of breakthrough pain in patients using opioid therapy for chronic cancer pain.

The application was based on literature data on fentanyl, supplemented with pharmacokinetic data for Rapinyl and a comparison of Rapinyl bioavailability with Actiq lozenge, an authorised transmucosally administered fentanyl on demand. Pharmacokinetic characterisation following treatment with Rapinyl and pharmacokinetic comparisons of Rapinyl versus Actiq have been used as a basis for bridging to the extensive published data regarding clinical efficacy and safety data for authorized fentanyl products. Thus, only limited clinical data have been generated for the use of Rapinyl. A number of Concerned Member States considered that the bridging strategy was unacceptable and insufficient and that the fast dissolution of the Rapinyl tablet might be indicative of a higher Cmax and shorter Tmax. As a consequence, additional efficacy and safety data were required for the approval of Rapinyl for the management of breakthrough pain in the target population and the procedure was referred to the CHMP. The CHMP adopted a List of Questions (LoQ) to be addressed by the Applicant.

The Applicant provided an overview of the current knowledge of cancer breakthrough pain (BTP), describing the currently available treatment, and the published data and available safety and efficacy data for other fentanyl products, concluding that fentanyl is an ideal analgesic for treatment of breakthrough pain. Rapinyl is a rapidly disintegrating sublingual tablet designed to rapidly and predictably deliver fentanyl through the oral mucosa. A range of dose strengths allow individualised upward titration from the recommended starting dose to a dose that provides analgesia with acceptable side-effects. The Applicant has characterised the pharmacokinetic profile of Rapinyl by demonstrating rapid delivery, predictable PK over the proposed dose range and also showing that Rapinyl achieves similar plasma concentrations and pharmacokinetic profiles as Actiq at both low and high doses.

Similarly, the Applicant considered the clinical safety of fentanyl products to be well established and well tolerated in both volunteers and the target population and that the pattern of side effects was consistent with other fentanyl products, including those used for treating BTP. The Applicant provided data supporting the pharmacokinetic bridging strategy and demonstrating that fentanyl delivery from Rapinyl provides effective pain relief in the target population. A statistically significant decrease in pain intensity was achieved and clinically important decreases in pain occurred more rapidly in patients treated with Rapinyl compared to placebo. The Applicant concluded that Rapinyl is safe and well tolerated in patients, with an appropriate safety-profile of Rapinyl for this indication.

The Applicant further considered the current bridging strategy to be appropriate for the approval of Rapinyl over the 100-800µg dose range for the treatment of BTP in patients as Rapinyl delivers fentanyl within a plasma concentration range already established as safe and effective. The pharmacokinetics of Rapinyl are dose proportional and predictable with single and multiple dosing and this simple and quick to administer formulation therefore fulfils an unmet need for a product indicated for the treatment of breakthrough pain in cancer patients. The Applicant also described the proposed Risk Management Plan, the amendments to the Product Information and the education programme directed at healthcare professionals, patients and carers to be introduced at product launch. The Applicant therefore believes the benefit/risk for Rapinyl to be positive and that the outcome of any further clinical safety and efficacy studies with Rapinyl are predictable and hence, unnecessary. In addition, the sponsor provided a number of independent overwhelmingly positive benefit/risk judgements from experts in palliative care.

The CHMP not endorse the Applicant claims of dose-relationship between Rapinyl and Actiq and therefore could not conclude on the comparability of systemic exposure obtained with Rapinyl and

Actiq. The CHMP also considered it necessary to assess the full report of the analysis on the comparability of Rapinyl and Actiq, as the available PK data could not support the similarity of both products. Therefore the efficacy/safety profile of Rapinyl could be established.

The CHMP agreed that the pharmacodynamic properties and the effectiveness of fentanyl are well established and noted the pain model in BTP. Considering the narrow therapeutic margin of fentanyl, the efficacy/safety profile is tightly dependant on systemic exposure to this drug and as a consequence the comparability of systemic exposure is pivotal. Furthermore, the CHMP was not convinced by the Applicant claim of bioavailability of fentanyl comparison between Rapinyl and Actiq, requesting a robust demonstration of similarity in systemic exposure. The CHMP considered the low adverse spectrum incidence in opioid-tolerant patients reassuring and noted the statement in the SPC on dose titration. The reasonably low intra-individual variation in fentanyl plasma concentrations was also noted, including variation related to fluid intake, mouth wounds, xerostomia (dry mouth) and mucositis. However, the CHMP still considers that the safety of Rapinyl needs further clarification, in particular with regards to repeated administration, the 800 µg dose and the dose titration.

In conclusion, the CHMP considered that the Applicant provided limited information on the patient treatment (titration towards an efficient dose, multiple administrations, administration up to the highest dosage) which prevented an evaluation of efficacy and safety of Rapinyl in the clinical setting and characterisation of the full clinically relevant time effect profile of the drug. Therefore, although the CHMP considers that Rapinyl could be used for the treatment of breakthrough pain in cancer patients the combined available pharmacokinetic, pharmacological and clinical data were considered insufficient and the CHMP requested the Applicant to provide clinical demonstration of the efficacy and safety of Rapinyl at the proposed dosages, including the highest one.

The Applicant provided data from a study investigating the pharmacokinetics of Rapinyl in 8 opioid tolerant cancer patients, which demonstrated that the pharmacokinetic parameters in patients were not different from those in healthy volunteers, with a similar pharmacokinetic variability. The Applicant also discussed xerostomia and mucositis and was of the opinion that neither was expected to significantly affect the dissolution or absorption of sublingual Rapinyl, although noting that Rapinyl was not expected to be used in patients with severe mucositis.

The CHMP considered that while there are no reasons to suspect that individualised dose titration would not work for the majority of the patients, the CHMP noted that the highest dose was not studied and considered the study size (n=8) to be too small to draw any reliable conclusions due to the limited number of observations and the absence of statistical analysis of the available data. The CHMP therefore concluded that the comparability of patients to healthy volunteers was not demonstrated.

Conclusion on LoQ

In conclusion, the CHMP noted that no new data was provided by the Applicant during the procedure but disagreed with the Applicant point of view that further clinical efficacy and safety data are not needed, indeed the justification relies entirely on a bridging strategy that assumes that the bioavailability obtained with Rapinyl is twice higher than that obtained with Actiq at the same molar dose. The CHMP considered that this was not demonstrated by the data provided due to the questionability of the reliability of study EN3267-001, because the data does not allow the evaluation of the bioavailability of the two formulations, and because the pooled analysis cannot be endorsed. Furthermore, the CHMP considered that the provided clinical data on the efficacy and safety of Rapinyl in the treatment of BTP under normal conditions are scarce and that no conclusion could be drawn from the clinical study provided. In addition, because limited PK data are available in patients, these data cannot be compared to the ones obtained in healthy volunteers. Therefore, the CHMP was unable to agree that the safety and efficacy profile of Rapinyl could be anticipated from the provided documentation. In conclusion, the CHMP requested additional data supporting the efficacy and safety of Rapinyl (independently of Actiq) in the treatment of BTP and adopted a List of Outstanding Issues.

Responses to the LoOI and CHMP assessment

The Applicant was able to provide in the response to the LoOI the interim analyses from 2 ongoing Phase III safety and efficacy clinical studies (EN3267-005 and EN3267-007), performed in the US by Endo. The data submitted builds on clinical data from 221 volunteers and 41 patients. The Applicant also provided data demonstrating that Rapinyl met the primary efficacy endpoint (Sum of Pain Intensity Difference from baseline to 30 minutes (SPID30)) and that the results were highly statistically significant (p=0.0004). In addition, a clinically relevant time-effect profile appropriate for an episode of breakthrough painl and meaningful clinical benefits for the patients were shown; patients could identify an effective dose of Rapinyl and use it successfully to control multiple episodes of breakthrough pain. The Applicant concluded that an optimal dose of Rapinyl provides a rapid onset of analgesia which mirrors the profile of cancer breakthrough pain. The Applicant considered the rate and extent of absorption to be similar for Rapinyl and Actiq and that the similarity in the PK profiles during the first 30-minute rapid absorption phase is established. Furthermore, the data generated for Rapinyl and the substantial additional cancer patient exposure data demonstrate that volunteers and patients have similar pharmacokinetics, negating the need for additional studies in healthy volunteers.

The Applicant considered that Rapinyl can be successfully titrated and repeatedly administered effectively and safely to treat patients with multiple episodes of breakthrough pain. Safety data from EN3267-005 and EN3267-007 have also been provided based on an interim cut of the safety database in January 2008, comprising only serious adverse events (SAEs). Up to this date there were no reports of any SAEs assessed as being related to Rapinyl in either study. As the safety of transmucosal fentanyl is well described, any relevant safety issues would have been observed as serious events. The Applicant also defended the 800ug dose and discussed the safety of Rapinyl when superimposed on a continuous fentanyl or non-fentanyl opioid pain therapy and considered that the transmucosal delivery of fentanyl produces consistent results, independent of the type of baseline therapy.

In conclusion, the Applicant considered that the results from studies EN3267-005 and EN3267-007 confirm the conclusions based on the original bridging strategy and demonstrate that Rapinyl can be safely and effectively used to treat multiple episodes of cancer breakthrough pain in opioid-tolerant patients. The Applicant believes that the original bridging strategy plus the significant body of confirmatory efficacy and safety data in cancer patients provided demonstrate that Rapinyl does indeed have a positive benefit-risk profile. Notwithstanding this, the Applicant remains committed to the proposed comprehensive risk management plan that will be put in place.

The CHMP acknowledged the data submitted, noting and assessing the data from the clinical studies EN3267-005 and EN3267-007. The main use of the referred interim analyses is in the detection of any new safety signals and as a comparison of the efficacy in relation to earlier findings. The CHMP considered that the information provided was sufficient for concluding that repeat dose data following Actiq and Rapinyl are similar, and the dose proportionalilty between Actiq and Rapinyl was considered as established through the single dose data, pending further clinical safety and efficacy data. The CHMP also agreed that the proposed dose range for Rapinyl is sufficiently documented and that further efficacy and safety data on dose titration is not necessary. In addition, there is solid experience in treating BTP in patients with chronic cancer already receiving a stable dose of background analgesia with strong opioids. However, although the interim data support the proposed dose range for Rapinyl, the CHMP requested additional clinical data clearly demonstrating the efficacy/safety of Rapinyl. The CHMP considered the pharmacokinetic data in healthy volunteers vs. patients to be limited; however it agreed that the available data do not indicate alarming differences.

The CHMP considered that while the efficacy data showed statistically significant difference in favour of Rapinyl versus placebo on SPID 30, the CHMP considered that the primary endpoints should include the assessment of pain intensity difference by simple scale and to define responder. In this study, the primary criteria chosen (SPID) and the time chosen for assessment of efficacy (30 min) do not seem appropriate to evaluate the efficacy of a treatment on BTP episodes, which are known to present a median duration of 30 min. The CHMP was of the opinion that the Applicant should provide an analysis of the percentage of 30% and 50% responders at 10 and 15 minutes in order to better evaluate the clinically relevant time-effect profile. Furthermore, while the reasons given by the

Applicant for analyzing only SAEs at this stage are endorsed, and the absence of new important safety issues was considered re-assuring by the CHMP, a full safety analysis should be provided by the Applicant. Finally, the CHMP considered that the database on efficacy and safety of Rapinyl in the treatment of cancer patients with BTP is rather poor and requested further safety analyses to be provided: detailed exposition of patients to Rapinyl, full safety analysis, narratives of the deaths.

Based on the review of the data and the responses, the CHMP considered the application for Rapinyl to be approvable, provided that the Applicant addressed the List of Remaining Issues satisfactorily.

Responses to the Remaining Issues and CHMP assessment

The Applicant confirmed that the tablets used in the Endo Phase III studies, EN3267-005 and EN3267-007, are qualitatively and quantitatively identical to the tablets currently under review in Europe and that the manufacturing process is the same using fentanyl citrate from the same supplier, with identical specifications. This allows the extrapolation of the conclusions from these studies to Rapinyl. The CHMP agreed and considered the issue to be resolved.

The Applicant provided further reassurances on the use of Rapinyl in patiens with mucositis, based on publications and guidelines, concluding that patients with mild/moderate mucositis can use oral medication, while transmucosal forms of fentanyl are not suitable for use in patients with severe mucositis where other routes of analgesia administration are preferable. The Applicant implemented a revised a cautionary statement in section 4.4 of the SPC, recommending extra caution during the titration of patients with mouth wounds or mucositis. The Applicant further described data from the time of the safety cut-off (Jan-08) and considered that the derived information compared favourably to values quoted for Effentora and Actiq, although the reason for patient drop-out was not provided by the sponsor. In addition, the oral cavity was inspected by the clinician or nurse 15-20 minutes after treatment to check for local irritation, no abnormal results were identified and the tablets were well tolerated after both single and repeat doses. The CHMP considered that the number of patients successfully titrating to an effective dose is close to the one observed for both Actiq and Effentora and observed that as 97% of the patients successfully titrating to an effective dose were able to complete the randomisation phase of the study, no particular safety issues were identified.

The Applicant referred to the provided analysis of Pain Intensity Difference (PID) for Rapinyl compared to placebo from the 10 minute time point in the EN3267-005 study. While no analysis of 30% and 50% responders at 10 and 15 minutes was conducted in the interim analysis, this analysis was requested from the sponsor in the final clinical study report. In the absence of the data, the Applicant provided data demonstrating a direct correlation between 33% responder analysis and PID, and used the current available pain data and the PID values to estimate the responder rates between active and placebo treatment at earlier time points. While not validated, the results obtained from the extrapolations compared favourably to Effentora and Actiq. In conclusion, the Applicant believes that the demonstration of a statistically significant improvement in PID at 10 and 15 minutes in EN3267-005 is the appropriate, clinically relevant measure of the early effectiveness of Rapinyl, and that an improvement in PID is directly reflected in an increase in responder rate. The Applicant also presented and extensively discussed exposure data for the 131 patients that successfully titrated in studies EN3267-005 and 007 and for the patients completing the 3 and 12-month follow-up periods.

The Applicant discussed the previously provided SAE dataset up to the 18th January 2008 safety cut-off and considered that the new safety data supplemented the bridging strategy and was in line with a further review of SAE data up to the 15th May-08. The Applicant described the observed SAE signals and noted that only one case was evaluated as related to the study drug by the investigator.. The Applicant also discussed the difference between the volunteers (opioid-naïve) and the target patient population (chronic opioid users), noting that the pattern of related events was consistent with available literature on the safety profile of fentanyl products and the absence of dose-related trends in the incidence of adverse events. A large number of Rapinyl doses have been administered during these Phase III studies and high doses of Rapinyl have been used for long periods of administration without any cause for concern over the nature and frequency of reported SAEs. Thus the Applicant considered the safety-profile of Rapinyl to be appropriate for this indication. The CHMP was reassured by the

absence of safety signals related to SAEs were reported but requested the Applicant to submit a full safety analysis as conditions to the Marketing Authorisations.

The Applicant provided the case narratives for all the deaths notified to the Applicant and reviewed the adverse events with an outcome of death, and concluded that these deaths not considered as related to the study drug by the study investigators. One patient had a successful suicide attempt but while suicidal ideation is known to be more common in patients with cancer than in the general population, neither suicide nor suicidal ideation has been reported as an adverse event associated with Actiq nor with Fentora/Effentora and based on the similar pharmacokinetic profile of Rapinyl and Actiq, the Applicant believes that this was a sporadic case, consistent with the investigator's assessment as being unrelated. The CHMP reviewed the death narratives and agreed with the Applicant conclusions. However, the successful suicidal attempt requires attention, and because depression and mood liability are adverse events listed in the SPC of Actiq, the CHMP considered that these kinds of events should be closely monitored and requested the issue to be followed up in post-marketing Pharmacovigilance.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The CHMP welcomed the new interim analyses of efficacy and safety data for Rapinyl, but considered that the new data must be regarded as preliminary data, as the complete trial results are not yet available for assessment. Even though the number of patients analysed is rather low, information is now available on the treatment of BTP in cancer patients at a dose range from 100 µg up to 800 µg and there were no new safety signals. This was supported by the known properties of fentanyl, the submitted clinical data, the revised SPC version recommending strict individual dose titration, and the proposed Risk Management Plan.

The efficacy data show that Rapinyl is statistically different from placebo in the treatment of BTP and these results seem clinically relevant. An extrapolation of the PID at 10 and 15 minutes to responder rates has been provided by the Applicant. This calculation seems reasonable, however, responder analysis should be provided when available. The available data on exposition was provided as requested and even if the data are not the definitive ones, the CHMP considered that exposure to Rapinyl is sufficient at this point in time. Due to the low number of patients exposed for a long time, the final results of the studies EN3267-005 and EN3267-007 should be provided as conditions to the Marketing Authorisations. From the efficacy and safety data provided, Rapinyl seems to be comparable to other fentanyl containing products (Actiq and Effentora) for the treatment of BTP in cancer patients.

However, due to the quite low number of patients exposed for a long time, the Applicant was asked to provide the final results of the studies EN3267-005 and EN3267-007 and the full safety analysis data on SAEs as conditions to the Marketing Authorisations. In addition, the suicidality should be monitored, as depression and mood liability are part of the reported AEs for Actiq.

In conclusion, the CHMP considered that the Applicant had answered the questions adequately. Based on the review of the data and on the Applicant responses to list of outstanding issues and to the remaining issues, the CHMP considered the benefit/risk ratio of Rapinyl to be positive and the application for Rapinyl sublingual tablet 50, 100, 200, 300, 400, 600 and 800 µg to be approvable, provided that the Applicant implements the amendments made to the text of the Product Information and fulfills the conditions to the Marketing Authorisation as described in Annex IV.

Whereas

- the responses provided by the Applicant, in particular the additional clinical data submitted during the CHMP referral procedure, successfully addressed the CHMP concerns,

- the dose range of Rapinyl and the dose proportionalilty between Actiq and Rapinyl was considered as established

- and provided that the Applicant fulfils the conditions to the Marketing Authorisation as listed in Annex IV

- the CHMP considered the benefit/risk of Rapinyl to be positive

the CHMP has recommended the amendment of the Summaries of Product Characteristics and the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Rapinyl and associated names (see Annex I). The conditions to the Marketing Authorisation as listed in Annex IV.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rapinyl and associated names (see Annex I) 50 microgram sublingual tablets
[See Annex I - To be completed nationally]

Rapinyl 100 microgram sublingual tablets
Rapinyl 200 microgram sublingual tablets
Rapinyl 300 microgram sublingual tablets
Rapinyl 400 microgram sublingual tablets
Rapinyl 600 microgram sublingual tablets
Rapinyl 800 microgram sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 50 micrograms fentanyl (as citrate)
100 micrograms fentanyl (as citrate)
200 micrograms fentanyl (as citrate)
300 micrograms fentanyl (as citrate)
400 micrograms fentanyl (as citrate)
600 micrograms fentanyl (as citrate)
800 micrograms fentanyl (as citrate)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

50 microgram sublingual tablet is a white pentagon-shaped tablet
100 microgram sublingual tablet is a white round tablet
200 microgram sublingual tablet is a white oval-shaped tablet
300 microgram sublingual tablet is a white triangle-shaped tablet
400 microgram sublingual tablet is a white diamond-shaped tablet
600 microgram sublingual tablet is a white "D"-shaped tablet
800 microgram sublingual tablet is a white capsule-shaped tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

4.2 Posology and method of administration

Rapinyl should only be administered to patients who are considered tolerant to their opioid therapy for persistent cancer pain. Patients can be considered opioid tolerant if they take at least 60 mg oral morphine per day, 25 micrograms transdermal fentanyl per hour, or an equianalgesic dose of another opioid for a week or longer.

Rapinyl sublingual tablets should be administered directly under the tongue at the deepest part. Rapinyl sublingual tablets should not be swallowed, but allowed to completely dissolve in the

sublingual cavity without chewing or sucking. Patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved.

In patients who have a dry mouth water may be used to moisten the buccal mucosa before taking Rapinyl.

Dose titration:

The optimal dose of Rapinyl will be determined by upward titration, on an individual patient basis. Several doses are available for use during the dose titration phase. The initial dose of Rapinyl used should be 100 micrograms, titrating upwards as necessary through the range of available dosage strengths.

The 50 microgram strength sublingual tablet may be used for an intermediate dose-titration step.

Patients should be carefully monitored until an appropriate dose is reached, i.e. that provides adequate analgesia with acceptable adverse reactions for each episode of breakthrough pain.

Switching from other fentanyl containing products to Rapinyl must not occur at a 1:1 ratio because of different absorption profiles. If patients are switched from another fentanyl containing product, a new dose titration with Rapinyl is required.

The following dose regimen is recommended for titration, although in all cases the physician should take into account the clinical need of the patient, age and concomitant illness.

All patients must start therapy with a single 100 microgram sublingual tablet. If adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram sublingual tablet may be administered. If inadequate pain relief is obtained with 2 x 100 microgram sublingual tablets, an increase in dose to the next higher available strength for the next episode of breakthrough pain should be considered. Dose escalation should continue in a stepwise manner until adequate analgesia is achieved. This titration should follow the course of administering a single sublingual tablet, with administration of a supplemental second sublingual tablet after 15-30 minutes, if inadequate pain relief is obtained. The dose strength for the supplemental sublingual tablet should be increased from 100 to 200 micrograms at doses of 400 micrograms and higher. This is illustrated in the schedule below. No more than two (2) sublingual tablets should be administered for a single episode of breakthrough pain during this titration phase.

Strength (micrograms) of first sublingual tablet per episode of breakthrough pain	Strength (micrograms) of supplemental (second) sublingual tablet to be taken 15-30 minutes after first tablet, if required
100	100
200	100
300	100
400	200
600	200
800	-

If adequate analgesia is achieved at the higher dose, but undesirable effects are considered unacceptable, an intermediate dose (using the 50 microgram or 100 microgram sublingual tablet where appropriate) may be administered.

Doses higher than 800 micrograms have not been evaluated in clinical studies.

In order to minimise the risk of opioid–related adverse reactions and to identify the appropriate dose, it is imperative that patients be monitored closely by health professionals during the titration process.

Maintenance therapy:
Once an appropriate dose has been established, which may be more than one tablet, patients should be maintained on this dose and should limit consumption to a maximum of four Rapinyl doses per day.

Dose re-adjustment:
If the response (analgesia or adverse reactions) to the titrated Rapinyl dose markedly changes, an adjustment of dose may be necessary to ensure that an optimal dose is maintained.
If more than four episodes of breakthrough pain are experienced per day over a period of more than four consecutive days, then the dose of the long acting opioid used for persistent pain should be re-evaluated. If the long acting opioid or dose of long acting opioid is changed the Rapinyl dose should be re-evaluated and re-titrated as necessary to ensure the patient is on an optimal dose.

It is imperative that any dose re-titration of any analgesic is monitored by a health professional.

Discontinuation of therapy:
For patients no longer requiring any opioid therapy, the Rapinyl dose should be taken into consideration before a gradual downward titration of opioids to minimise possible withdrawal effects.

In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, Rapinyl therapy may usually be discontinued immediately.

Use in children and adolescents:
Rapinyl must not be used in patients less than 18 years of age due to a lack of data on safety and efficacy.

Use in elderly patients
Dose titration needs to be approached with particular care and patients observed carefully for signs of fentanyl toxicity (see section 4.4).

Use in patients with renal and hepatic impairment
Patients with kidney or liver dysfunction should be carefully observed for signs of fentanyl toxicity during the Rapinyl titration phase (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Opioid-naïve patients because of the risk of life-threatening respiratory depression.

Severe respiratory depression or severe obstructive lung conditions.

4.4 Special warnings and precautions for use

Patients and their carers must be instructed that Rapinyl contains an active substance in an amount that can be fatal to a child, and therefore to keep all tablets out of the reach and sight of children.

Due to the potentially serious undesirable effects that can occur when taking an opioid therapy such as Rapinyl, patients and their carers should be made fully aware of the importance of taking Rapinyl correctly and what action to take should symptoms of overdose occur.
Before Rapinyl therapy is initiated, it is important that the patient's long-acting opioid treatment used to control their persistent pain has been stabilised.

Upon repeated administration of opioids such as fentanyl, tolerance and physical and/or psychological dependence may develop. Iatrogenic addiction following therapeutic use of opioids is rare.

In common with all opioids, there is a risk of clinically significant respiratory depression associated with the use of Rapinyl. Particular caution should be exercised during dose titration with Rapinyl in patients with chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression (e.g. myasthenia gravis) because of the risk of further respiratory depression, which could lead to respiratory failure.

Rapinyl should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of hyperkapnia, such as those showing evidence of raised intracranial pressure, reduced consciousness, coma or brain tumours. In patients with head injuries, the clinical course may be masked by the use of opioids. In such a case, opioids should be used only if absolutely necessary.

Intravenous fentanyl has been shown to cause bradycardia. Rapinyl should be used with caution in patients with bradyarrhythmias.

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to the active substance than younger patients. Elderly, cachectic, or debilitated patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Rapinyl should be administered with caution to patients with liver or kidney dysfunction, especially during the titration phase. The use of Rapinyl in patients with hepatic or renal impairment may increase the bioavailability of fentanyl and decrease its systemic clearance, which could lead to accumulation and increased and prolonged opioid effects.

Care should be taken in treating patients with hypovolaemia and hypotension.

Rapinyl has not been studied in patients with mouth wounds or mucositis. There may be a risk of increased systemic drug exposure in such patients and therefore extra caution is recommended during dose titration.

There should be no noticeable effects on cessation of treatment with Rapinyl, but possible symptoms of withdrawal are anxiety, tremor, sweating, paleness, nausea and vomiting.

4.5 Interaction with other medicinal products and other forms of interaction

Fentanyl is metabolised by CYP3A4. Active substances that inhibit CYP3A4 activity such as macrolide antibiotics (e.g. erythromycin), azole antifungal agents (e.g. ketoconazole, itraconazole) or certain protease inhibitors (e.g. ritonavir) may increase the bioavailability of fentanyl by decreasing its systemic clearance, potentially enhancing or prolonging opioid effects. Grapefruit juice is also known to inhibit CYP3A4. Fentanyl should therefore be given to patients with caution if administered concomitantly with CYP3A4 inhibitors.

Concomitant use of other CNS depressants, such as other morphine derivatives (analgesics and antitussives), general anaesthetics, skeletal muscle relaxants, sedative antidepressants, sedative H1 antihistamines, barbiturates, anxiolytics (ie benzodiazepines), hypnotics, antipsychotics, clonidine and related substances may produce increased CNS depressant effects. Respiratory depression, hypotension and profound sedation may occur.

Alcohol potentiates the sedative effects of morphine-based analgesics, therefore concomitant administration of alcoholic beverages or medicinal products containing alcohol with Rapinyl is not recommended.

Rapinyl is not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

The concomitant use of partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients.

4.6 Pregnancy and lactation

The safety of fentanyl in pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Fentanyl should only be used during pregnancy when clearly necessary.

Long-term treatment during pregnancy may cause withdrawal symptoms in the new-born infant.

Fentanyl should not be used during labour and delivery (including caesarean section) since fentanyl crosses the placenta and may cause respiratory depression in the foetus or in the new-born infant.

Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should only be used by breast-feeding women if the benefits clearly outweigh the potential risks for both mother and child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, fentanyl may impair the mental or physical ability to perform potentially hazardous tasks such as driving or operating machinery. Patients should be advised not to drive or operate machinery if they become dizzy or drowsy or experience blurred or double vision while taking Rapinyl.

4.8 Undesirable effects

Undesirable effects typical of opioids are to be expected with Rapinyl; they tend to decrease in intensity with continued use. The most serious potential adverse reactions associated with opioid use are respiratory depression (which could lead to respiratory arrest), hypotension and shock. Other very commonly reported adverse reactions include: nausea, vomiting, constipation, headache, somnolence/fatigue and dizziness.

Adverse reactions from clinical studies with Rapinyl in patients and volunteers, with a suspected relationship to treatment, are listed below by system organ class and frequency (very common ≥ 1/10; common ≥ 1/100 to < 1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Very common: Dizziness, somnolence, headache
Common: Vasovagal reaction, hypoaesthesia, paraesthesia, hyperacusis

Eye disorders
Common: Vision abnormal

Respiratory, thoracic and mediastinal disorders
Common: Respiratory depression, rhinitis, pharyngitis

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, abdominal pain, diarrhoea, constipation, stomach discomfort, dyspepsia, dry mouth

Skin and subcutaneous tissue disorders
Common: Rash, pruritus

Vascular disorders
Common: Orthostatic hypotension, flushing, hot flush

General disorders and administration site conditions
Very common: Fatigue
Common: Asthenia, application site irritation

Psychiatric disorders
Common: Depression, anorexia, concentration impaired, euphoria

All the above adverse reactions were reported in opioid naïve volunteers administered with Rapinyl. Patients (n=23) treated with Rapinyl only experienced dizziness, nausea and vomiting.

The following adverse reactions associated with other medicinal products containing fentanyl have also been reported (very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1000 to < 1/100; rare ≥ 1/10,000 to < 1/1000; very rare < 1/10,000; not known (cannot be estimated from available data)):

Cardiac disorders
Uncommon: Bradycardia, tachycardia, hypertension
Very rare: Arrhythmias

Nervous system disorders
Common: Myoclonus, insomnia, taste disorders
Uncommon: Abnormal gait/coordination, vertigo, amnesia, speech disorders, tremor

Respiratory thoracic and mediastinal disorders
Uncommon: Hypoventilation, asthma, dyspnoea,
Very rare: Apnoea, haemoptysis

Gastrointestinal disorders
Common: Gastro-intestinal occlusion, dysphagia, mouth ulcers/stomatitis, tongue disorder
Uncommon: Enlarged abdomen, flatulence, thirst
Rare: Hiccups

Renal and urinary disorders
Uncommon: Urinary retention, change in urinary frequency
Very rare: bladder spasm, oliguria

Skin and subcutaneous tissue disorders
Very common: Sweating

Injury, poisoning and procedural complications
Common: Accidental injuries

Vascular disorders
Common: Vasodilation

General disorders and administration site conditions
Uncommon: Malaise

Psychiatric disorders
Common: Hallucinations, confusion, anxiety, nervousness, abnormal thinking, abnormal dreams
Uncommon: Agitation, depersonalisation, emotional lability

4.9 Overdose

The symptoms of fentanyl overdose are an extension of its pharmacological actions, the most serious effect being respiratory depression, which may lead to respiratory arrest.

Management of opioid overdose in the immediate term includes removal of any remaining Rapinyl sublingual tablets from the mouth, physical and verbal stimulation of the patient and an assessment of the level of consciousness. A patent airway should be established and maintained. If necessary an oropharyngeal airway or endotracheal tube should be inserted, oxygen administered and mechanical ventilation initiated, as appropriate. Adequate body temperature and parenteral fluid intake should be maintained.

For the treatment of accidental overdose in opioid-naïve individuals, naloxone or other opioid antagonists should be used as clinically indicated and in accordance with their Summary of Product Characteristics. Repeated administration of the opioid antagonist may be necessary if the duration of respiratory depression is prolonged.

Care should be taken when using naloxone or other opioid antagonists to treat overdose in opioid-maintained patients, due to the risk of precipitating an acute withdrawal syndrome.

If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

Muscle rigidity interfering with respiration has been reported with fentanyl and other opioids. In this situation, endotracheal intubation, assisted ventilation and administration of opioid antagonists as well as muscle relaxants may be requested.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Phenylpiperidine derivatives, ATC code: N02ABO3

Fentanyl is a potent μ-opioid analgesic with rapid onset of analgesia and short duration of action. Fentanyl is approximately 100-fold more potent than morphine as an analgesic. Secondary effects of fentanyl on central nervous system (CNS), respiratory and gastro-intestinal function are typical of opioid analgesics and are considered to be class effects.

The analgesic effects of fentanyl are related to the blood level of the active substance; in opioid-naïve patients, minimum effective analgesic serum concentrations of fentanyl range from 0.3-1.2 ng/ml, while blood levels of 10-20 ng/ml produce surgical anaesthesia and profound respiratory depression.

In patients with chronic cancer pain on stable maintenance doses of opioids, Rapinyl has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards, with a significantly lower need for rescue analgesic therapy. The safety and efficacy of Rapinyl have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Rapinyl for predictable pain episodes was not investigated in the clinical trials.

Fentanyl, in common with all μ-opioid receptor agonists, produces dose dependent respiratory depression. This risk is higher in opioid-naïve subjects than in patients experiencing severe pain or receiving chronic opioid therapy. Long-term treatment with opioids typically leads to development of tolerance to their secondary effects.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract leading to a prolongation in gastrointestinal transit time, which may be responsible for the constipating effect of fentanyl.

5.2 Pharmacokinetic properties

Fentanyl is a highly lipophilic drug absorbed very rapidly through the oral mucosa and more slowly through the gastrointestinal tract. Orally administered fentanyl undergoes pronounced hepatic and intestinal first pass effects.

Rapinyl is a quick dissolving sublingual tablet formulation. Rapid absorption of fentanyl occurs over about 30 minutes following administration of Rapinyl. The bioavailability of Rapinyl has not been studied but is estimated to be about 70%. Mean maximal plasma concentrations of fentanyl range from 0.2 to 1.3 ng/ml (after administration of 100 to 800 µg Rapinyl) and are reached within 22.5 to 240 minutes.

About 80-85% of fentanyl is bound by plasma proteins, mainly α1-glycoprotein and to a lesser extent albumin and lipoprotein. The volume of distribution of fentanyl at steady state is about 3-6 l/kg.

Fentanyl is metabolised primarily via CYP3A4 to a number of pharmacologically inactive metabolites, including norfentanyl. Within 72 hours of intravenous fentanyl administration around 75% of the dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites. Total plasma clearance of fentanyl is about 0.5 l/h/kg. After Rapinyl administration, the main elimination half-life of fentanyl is about 7 hours (range 3-12.5 hours) and the terminal half-life is about 20 hours (range 11.5-25 hours).

The pharmacokinetics of Rapinyl have been shown to be dose proportional over the dose range of 100 to 800 µg.

Renal/hepatic impairment
Impaired hepatic or renal function could cause increased serum concentrations. Elderly, cachectic or generally impaired patients may have a lower fentanyl clearance, which could cause a longer terminal half-life for the compound (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Safety pharmacology and repeated dose toxicity data reveal no special hazard for humans that is not already covered by other sections of this SPC. Animal studies have shown reduced fertility and increased mortality in rat foetuses. Teratogenic effects have, however, not been demonstrated.

Mutagenicity testing in bacteria and in rodents yielded negative results. Like other opioids fentanyl showed mutagenic effects *in vitro* in mammalian cells. A mutagenic risk with therapeutic use seems unlikely since effects were induced only at very high concentrations.

Long-term carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Silicified microcrystalline cellulose
Croscarmellose sodium

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original blister package in order to protect from moisture.

6.5 Nature and contents of container

Rapinyl sublingual tablets are packaged in OPA/PVC/aluminium/aluminium blisters contained in a cardboard outer carton. The packaging is colour-coded for each Rapinyl sublingual tablet strength.

Pack size: Packs of 10 or 30 sublingual tablets. Not all pack sizes may be marketed

6.6 Special precautions for disposal

Waste material should be disposed of safely. Patients/carers should be encouraged to return any unused product to the Pharmacy, where it should be disposed of in accordance with national and local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label

1. NAME OF THE MEDICINAL PRODUCT

Rapinyl and associated names (see Annex I) 50 microgram sublingual tablets
[See Annex I - To be completed nationally]
Rapinyl 100 microgram sublingual tablets
Rapinyl 200 microgram sublingual tablets
Rapinyl 300 microgram sublingual tablets
Rapinyl 400 microgram sublingual tablets
Rapinyl 600 microgram sublingual tablets
Rapinyl 800 microgram sublingual tablets

Fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 50 micrograms fentanyl (as citrate)
100 micrograms fentanyl (as citrate)
200 micrograms fentanyl (as citrate)
300 micrograms fentanyl (as citrate)
400 micrograms fentanyl (as citrate)
600 micrograms fentanyl (as citrate)
800 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

10 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Sublingual use.
To be dissolved under the tongue.
Do not swallow
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This product should ONLY be used as prescribed. If the product is used by anyone else it could represent a SERIOUS risk to their health

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Store in the original blister package in order to protect from moisture

It is recommended to keep Rapinyl in a locked storage space

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused product should be taken, if possible, to your pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Rapinyl 50 micrograms
Rapinyl 100 micrograms
Rapinyl 200 micrograms
Rapinyl 300 micrograms
Rapinyl 400 micrograms
Rapinyl 600 micrograms
Rapinyl 800 micrograms

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Rapinyl and associated names (see Annex I) 50 µg sublingual tablets
[See Annex I - To be completed nationally]
Rapinyl 100 µg sublingual tablets
Rapinyl 200 µg sublingual tablets
Rapinyl 300 µg sublingual tablets
Rapinyl 400 µg sublingual tablets
Rapinyl 600 µg sublingual tablets
Rapinyl 800 µg sublingual tablets

Fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Rapinyl and associated names (see Annex I) **50 microgram sublingual tablets**
[See Annex I - To be completed nationally]
Rapinyl 100 microgram sublingual tablets
Rapinyl 200 microgram sublingual tablets
Rapinyl 300 microgram sublingual tablets
Rapinyl 400 microgram sublingual tablets
Rapinyl 600 microgram sublingual tablets
Rapinyl 800 microgram sublingual tablets

Fentanyl

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT RAPINYL IS AND WHAT IT IS USED FOR

Rapinyl is a treatment for people **who must already regularly be taking strong pain-relieving medicine (opioids)** for their persistent cancer pain, but require treatment for their breakthrough pain. If you are not sure, talk to your doctor.

Breakthrough pain is pain which occurs suddenly, even though you have taken or used your usual opioid pain-relieving medicine.

The active substance in Rapinyl sublingual tablets is fentanyl. Fentanyl belongs to a group of strong pain-relieving medicines called opioids.

2. BEFORE YOU TAKE RAPINYL

Do not take Rapinyl

- if you are allergic (hypersensitive) to fentanyl or any of the other ingredients of Rapinyl
- if you have severe breathing problems

Before you start treatment with Rapinyl, **you must have been regularly taking or using a prescribed strong pain-relieving medicine, called an opioid, to control your persistent pain**. If you have not, this medicine could cause severe breathing difficulties (see section 4 – Possible side effects). If you are not sure, talk to your doctor.

Take special care with Rapinyl

Tell your doctor before treatment if you have or have recently had any of the following, as your doctor will need to take account of these when prescribing your dose:

- a head injury, because Rapinyl may cover up the extent of the injury
- breathing problems or suffer from myasthenia gravis (a condition characterised by muscle weakness)
- a slow heart rate or low blood pressure
- liver or kidney disease, as this may require your doctor to more carefully adjust your dose
- a brain tumour and/or raised intracranial pressure (an increase of pressure in the brain which causes severe headache, a feeling of sickness and blurred vision)
- mouth wounds or mucositis (swelling and redness of the inside of the mouth)

When taking Rapinyl, if you are to have any surgery, inform your doctor or dentist that you are taking this medicine.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines (other than your regular opioid pain-relieving medicine), including medicines obtained without a prescription.

The following medicines may increase the effects of Rapinyl:

- Certain types of antifungal medicines containing e.g. ketoconazole or itraconazole (used to treat fungal infections).
- Certain types of antibiotic medicines used to treat infections (called macrolides, containing e.g. erythromycin).
- Certain types of antiviral medicines used to treat infections caused by viruses (called protease inhibitors, containing e.g. ritonavir).
- Medicines containing alcohol
- Medicines called monoamine-oxidase (MAO) inhibitors, which are used for severe depression and Parkinson's disease. Tell your doctor if you have taken this type of medicine within the last two weeks

The following medicines may reduce the effects of Rapinyl:

- Certain types of strong pain killers containing e.g. buprenorphine or pentazocine

Rapinyl may add to the effect of medicines that make you feel sleepy, including:

- other **strong pain-relieving medicines** (opioid-type medicines e.g. for pain and cough)
- general anaesthetics (used to make you sleep during operations)
- muscle relaxants
- sleeping tablets
- medicines used to treat
  - depression
  - allergies
  - anxiety and psychosis
- medicines containing clonidine (used to treat high blood pressure).

Taking Rapinyl with food and drink

Rapinyl can make some people feel drowsy. Do not consume alcohol without consulting your doctor as it might make you feel more drowsy than usual.

Do not drink grapefruit juice while you are prescribed Rapinyl treatment as it may increase the side effects of Rapinyl.

Pregnancy and breast-feeding

You must not use Rapinyl during pregnancy unless you have been specifically told to by your doctor.

Fentanyl is passed on into breast milk and may cause extreme drowsiness and shallow breathing in the breastfed child. Consult your doctor and do not use Rapinyl during breast-feeding unless your doctor considers that the benefits for you are greater than the risks to the child.

Ask your doctor or pharmacist for advice before taking any medicine when pregnant or breast-feeding.

Driving and using machines

Rapinyl may impair your mental and/or physical ability to perform potentially hazardous tasks such as driving or operating machinery.

If you feel dizzy, sleepy or have blurred vision when you take Rapinyl, do not drive or use machinery.

3. HOW TO TAKE RAPINYL

Before taking Rapinyl for the first time your doctor will explain how Rapinyl should be taken to effectively treat your breakthrough pain.

Always take Rapinyl exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

This product should ONLY be used by you according to your doctor's instructions. It should not be used by anyone else as it could present a SERIOUS risk to their health, especially in children.

Initial Phase – Finding the most appropriate dose

For Rapinyl to work successfully, your doctor will need to identify the most appropriate dose for treating a single episode of breakthrough pain. Rapinyl sublingual tablets are available in a range of strengths. You may need to try different strengths of Rapinyl sublingual tablets over a number of episodes of breakthrough pain to find the most appropriate dose. Your doctor will help you do this and will work with you to find the best strength of tablet to use.

If you do not get adequate pain relief from one tablet your doctor may ask you to take two tablets to treat an episode of breakthrough pain. Do not take a second tablet unless your doctor tells you to as this may result in overdose. Your doctor will advise you which strength of tablet to use.

Rapinyl is a different type of medicine from other medicines you may have used to treat your breakthrough pain. **You must always use the dose of Rapinyl as prescribed by your doctor** – this may be a different dose from that which you have used with other medicines for breakthrough pain.

Maintenance Phase - Once you have found the most appropriate dose

Once you and your doctor have found a dose of Rapinyl tablets that controls your breakthrough pain you should take this dose no more than four times a day. **A dose of Rapinyl may consist of more than one tablet.**

If you think that the dose of Rapinyl that you are using is not controlling your breakthrough pain satisfactorily tell your doctor, as he may need to adjust your dose.

You must not change your dose of Rapinyl unless directed by your doctor.

Taking the medicine

Rapinyl should be used sublingually. This means that the tablet should be placed under the tongue where it dissolves rapidly in order to allow fentanyl to be absorbed across the lining of the mouth. Once absorbed, fentanyl starts to work to relieve pain.
When you get an episode of breakthrough pain, take the dose advised by your doctor as follows:

- If your mouth is dry, take a sip of water to moisten it. Spit out or swallow the water.
- Remove the tablet(s) from the blister pack immediately before use.
- Peel back the tab of the foil top of one blister and gently remove the tablet. Do not try to push Rapinyl sublingual tablets through the foil top, like a normal tablet
- Place the tablet under your tongue as far back as you can and let it dissolve completely.
- Rapinyl will dissolve rapidly under the tongue and be absorbed in order to provide pain relief. It is therefore important that you do not suck, chew or swallow the tablet.
- You should not drink or eat anything until the tablet has completely dissolved under your tongue.

If you take more Rapinyl than you should
- remove any remaining tablets from your mouth
- tell your carer or another person in your house what has happened
- you or your carer should immediately contact your doctor, pharmacist or local hospital and discuss what action to take
- while waiting for the doctor, keep the person awake by talking to or shaking her/him now and then

Symptoms of overdose include:
- extreme drowsiness
- slow, shallow breathing

If these occur, seek emergency medical help immediately.

If you think someone has taken Rapinyl by accident seek emergency medical help immediately.

If you stop taking Rapinyl
You should only stop taking Rapinyl sublingual tablets on the advice of your doctor. You must continue to take/use your regular opioid pain relieving medicine for persistent pain as advised by your doctor.

There should be no noticeable effects if you stop taking Rapinyl, but possible symptoms of withdrawal are anxiety, tremor, sweating, paleness, nausea and vomiting.

However, if you are concerned about your pain relief, you should talk to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Rapinyl can cause side-effects, although not everybody gets them.

If you start to feel unusually or extremely sleepy or your breathing becomes slow or shallow, you or your carer should immediately contact your doctor or local hospital for emergency help (see also section 3 "If you take more Rapinyl than you should").

Very common side effects (affects more than 1 user in 10) include:
- nausea, headache, sleepiness/tiredness, dizziness.

Common side effects (affects 1 to 10 users in 100) include:
- vomiting, diarrhoea, constipation, stomach ache, bloated feeling, indigestion, loss of appetite
- depression, difficulty in concentrating, excessive feeling of well being
- increased sensitivity to sound and noise, blurred or double vision
- low blood pressure, flushing/feeling hot, slow shallow breathing, feeling weak, feeling faint, reduced sensitivity to touch, numbness or tingling
- runny or blocked nose, dry mouth, sore throat, itching of the skin, skin rash, irritation under the tongue

Other known side effects associated with fentanyl products include:
- Very common side effects (affects more than 1 user in 10 people):
  excessive sweating
- Common side effects (affects 1 to 10 users in 100):
  feeling confused, feeling anxious or nervous, hallucinations, abnormal thinking, muscle twitching, difficulty sleeping, strange dreams, tongue or taste problems, flushing, mouth ulcers/blisters, blockage of the gut, difficulty swallowing, being accident-prone
- Uncommon side effects (affects 1 to 10 users in 1,000):
  feeling restless, feeling detached, moodswings, trembling, difficulty speaking, being forgetful, loss of coordination, vertigo, slow or fast heartbeat, high blood pressure, difficulty breathing, slow or shallow breathing, asthma, bloating, wind, thirst, difficulty going to the toilet, change in frequency of going to the toilet, feeling unwell
- Rare side effects (affects 1 to 10 users in 10,000):
  hiccups
- Very rare side effects (affects less than 1 user in 10,000):
  irregular heartbeat, stopping breathing, blood in the saliva, decrease in amount of urine, painful contraction of the bladder

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RAPINYL

The pain-relieving medicine in Rapinyl is very strong and could be life-threatening if taken accidentally by a child. Rapinyl must be kept out of the reach and sight of children.
Do not use Rapinyl after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Store in the original blister in order to protect from moisture.

It is recommended to keep Rapinyl in a locked storage space.

Any unused product should be taken, if possible, to your pharmacist to be disposed of safely. Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Rapinyl contains

The active substance is fentanyl. One sublingual tablet contains 50 micrograms fentanyl (as citrate)
100 micrograms fentanyl (as citrate)
200 micrograms fentanyl (as citrate)
300 micrograms fentanyl (as citrate)
400 micrograms fentanyl (as citrate)
600 micrograms fentanyl (as citrate)
800 micrograms fentanyl (as citrate)

The other ingredients are mannitol (E421), silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

What Rapinyl looks like and contents of the pack

Rapinyl is a small white sublingual tablet to be inserted under the tongue. It comes in a range of different strengths and shapes. Your doctor will prescribe the strength (shape) and number of tablets suitable for you.

The 50 microgram tablet is a white pentagon-shaped tablet.
The 100 microgram tablet is a white round tablet
The 200 microgram tablet is a white oval-shaped tablet
The 300 microgram tablet is a white triangle-shaped tablet
The 400 microgram tablet is a white diamond-shaped tablet
The 600 microgram tablet is a white “D”-shaped tablet
The 800 microgram tablet is a white capsule-shaped tablet

Rapinyl tablets are contained in blisters, available in cartons of 10 or 30 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

Marketing authorisation holder:
[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

Manufacturer:
Recip AB
Lagervägen 7
136 50 Haninge
Sweden
Tel. +46 8 6025200

This leaflet was last approved in {MM/YYYY}.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

The Applicant commits to provide the following information to the National Competent Authority of the Reference Member State:

- Analysis of the 30% and 50% responder rates at 10 and 15 minutes for the study EN-3267-005,

- Final results of studies EN3267-005 and 3267-007, including detailed exposure of patients and full safety analysis.