COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Submena 100, 200, 300, 400, 600 and 800 microgram, tablets for sublingual use (fentanyl citrate)

NL/H/5266/001-006/DC

Date: 31 January 2022

This module reflects the scientific discussion for the approval of Submena 100, 200, 300, 400, 600 and 800 microgram, tablets for sublingual use. The procedure was finalised on 26 August 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Submena, 100, 200, 300, 400, 600 and 800 microgram, tablets for sublingual use, from G.L. Pharma GmbH.

The product is indicated for 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Abstral 100/200/300/400/600/800 microgram sublingual tablets (NL RVG 108843-108848), which have been registered in the Netherlands by Kyowa Kirin Holdings B.V. since 2008 via the mutual recognition procedure (SE/H/0575/002-007).

The concerned member states (CMS) involved in this procedure were:
100 µg, 200 µg and 400 µg strengths - Austria, Bulgaria, Czech Republic, Denmark, Italy, Poland, Slovakia and Sweden.
300 µg strength - Italy and Sweden.
600 µg strength - Austria and Sweden.
800 µg strength - Austria, Czech Republic, Poland and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Submena are sublingual tablets, and their size, shape and colour differ according to strength:

- 100 microgram: white round tablet
- 200 microgram: white oval-shaped tablet
- 300 microgram: white triangle-shaped tablet
- 400 microgram: white diamond-shaped tablet
- 600 microgram: white “D”-shaped tablet
- 800 microgram: white capsule-shaped tablet

Each sublingual tablet contains fentanyl citrate equivalent to 100 µg, 200 µg, 300 µg, 400 µg, 600 µg or 800 µg micrograms of fentanyl.

The tablets are packed in child-resistant aluminium blisters (PA/Al/PVC), thermo-sealed to a foil (Al/PET) and contained in a cardboard outer carton.

The excipients are: mannitol (E421), microcrystalline cellulose (E460), colloidal silica anhydrous (E551), croscarmellose sodium (E468) and magnesium stearate (E470b).

The six tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is fentanyl citrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and is soluble in water, freely soluble in methanol, sparingly soluble in ethanol and very slightly soluble in methylene chloride. The active substance manufacturer consistently obtains the same crystalline form.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additionally, the finished product manufacturer controls the particle size and microbial quality of the drug substance. The proposed specification for the active substance by the finished product manufacturer is acceptable. The limits for the particle size are justified based on the active substance batch used for the batch for the bioequivalence study.

Batch analytical data demonstrating compliance with this specification have been provided for five batches. The batches tested were used in the manufacture of the finished product submission batches including the bio-batch.

The use of the Ph.Eur. reference standards for the identification and the determination of related substances in active substance as described in the monograph for fentanyl citrate is acceptable.

Stability of drug substance

The active substance is stable for 60 months when stored in double polyethylene bags placed in a HDPE drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. Formulation studies during product development have identified critical functionality related characteristics. A quality by design approach to product development was adopted in pre-formulation studies, screening and optimisation studies. The formulations of Fentanyl sublingual tablets are developed based on initial risk evaluation of the impact on the identified critical quality attributes of drug substance characteristics, formulation composition and manufacturing process.

Comparative dissolution studies between batches of the 300 µg drug product and reference product have been performed under different pH's. Dissolution for both test and reference product bio-batches is rapid and the dissolution profiles between test and reference products can be considered similar.

To support the application, the MAH has performed one bioequivalence study for the 300 µg strength of the finished product, and has requested a biowaiver for the other strengths. For the 100, 200, 400, 600 and 800 µg strengths of the finished product, similarity of the dissolution profiles with the 300 µg bio-batch strength was confirmed in all pH's tested. The batches used for the additional strengths are production scale batches that were also used for validation and stability studies.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The manufacturing process has been described in sufficient details. Briefly, the manufacturing process consists of a series of sieving and mixing of excipients followed by compression. Formulation development studies and risk assessments have defined operational ranges, which are in line with those used for validation batches. In-process controls are carried out on the uncoated tablets and the blister packed tablets. The test method and limits of the in-process controls have been described.

The justification for the identification of steps as critical have been provided, including a link to experimental data in the pharmaceutical development section. Mixing steps to ensure homogeneity of a low dose product are considered as critical.

The process is considered a non-standard process as the unit dose contains less than 2% active substance. The validation covered all manufactured strengths for production of the marketed product. However, a bracketing approach was used for the dose-proportional

strengths of 300, 400, 600 and 800 µg sublingual tablets. This is acceptable. The validation data provides assurance that the manufacturing process for the 100, 200, 300, 400, 600 and 800 µg sublingual tablets is capable of consistently producing a finished product that complies to all in-process and finished product specifications.

Process validation data on the product have been presented for three batches of the 100 µg, 200 µg, 300 µg and 800 µg tablets and for one batch of the 400 µg and 600 µg tablets, in accordance with the relevant European guidelines.

Control of excipients

Mannitol, croscarmellose sodium and magnesium stearate meet the specifications of the current Ph.Eur. Silicified microcrystalline cellulose complies with the United States Pharmacopeia (USP) requirements. These specifications are acceptable. The methods used for the testing of the excipients are compendial methods, therefore, there is no need for validation data. The MAH included specifications and the analytical method for particle size distribution of mannitol and silicified microcrystalline cellulose. The necessity of tests for functionality related characteristics for all excipients has been adequately discussed.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specifications includes tests for appearance, identity, uniformity of dosage units, degradation products, assay, disintegration and microbial purity. The release and shelf life limits are identical except for the limits of one impurity and of total degradation products. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The evaluation of elemental impurities in the drug product was performed according to the ICH. A risk evaluation for the potential presence of nitrosamines has been provided, all possible sources are taken into account and the conclusion that no risk is identified is endorsed.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed manufacturing site have been provided on three batches of the 100 µg, 200 µg, 300 µg and 800 µg tablets and for one batch of the 400 µg and 600 µg tablets. The results demonstrate compliance with the release specification.

Stability of drug products

Stability data on the product have been provided for three industrial scale batches for the 100, 200, 300 and 800 µg tablets in accordance with applicable European guidelines. The strengths of 300, 400, 600 and 800 µg tablets come from a common mixture which can be divided into the proposed range for tabletting the different strengths. For this common mixture the lowest and highest strengths have been introduced into the stability studies in accordance with ICH Q1D. Stability of the finished products packed in the container closure systems proposed for marketing was shown at 25°C/60% RH (up to 36 months) and at 40°C/75% RH (six months).

Also, a bulk product stability study, photostability study and forced degradation study were performed. The bulk product stability study demonstrated that the bulk remained stable for 12 months at long term conditions. Therefore, a holding time of six months is acceptable.

The photostability study was performed in accordance with ICH recommendations and indicated that there were no out of specification results for the parameters tested in samples directly exposed. Forced degradation studies confirmed that the proposed analytical method for degradation products can be considered as stability-indicating.

On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are: "Store in the original blister package in order to protect from moisture" and "This medicinal product does not require any special temperature storage conditions."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the products nor have any been used in the manufacturing of these products, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Submena has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Submena are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products are generic formulations of Abstral which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology,

pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fentanyl citrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study for the 300 µg strength. For the 100 µg, 200 µg, 400 µg, 600 µg and 800 µg strengths, a biowaiver has been requested. Both will be discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Submena 300 µg, tablets for sublingual use (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product Abstral 300 µg, tablets for sublingual use (Kyowa Kirin Limited, The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the drug test product and the reference product. The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

For safety and ethical reasons, the 300 µg tablet has been used in the bioequivalence study. The 'Guideline on the investigation of bioequivalence' indicates that for a drug with linear pharmacokinetics and which is highly soluble, a lower strength may be used in the bioequivalence study. These requirements are met, since fentanyl is highly soluble in water, and fentanyl is dose proportional over the dose range of 100 to 800 µg. As the sublingual tablet has to be absorbed in the oral cavity, the solubility in saliva is of importance as well. The amount of saliva is about 0.7 ml, which means that the highest dose of 800 µg will be still dissolved (yielding 1.1 mg/ml, whereas solubility in water/saliva is 25 mg/ml). With respect to this solubility, it is therefore acceptable as well to use the 300 µg tablet in the bioequivalence study. Overall, the use of the 300 µg tablet strength in the bioequivalence study has been justified.

Biowaiver

For the 100, 200, 400, 600 and 800 µg tablet strengths, a waiver was requested, with the 300 µg tablet strength as reference. All conditions for the biowaiver criteria have been met as per section 4.2.2 of CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**:

- The products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the 400, 600 and 800 µg strengths are quantitatively proportional to the 300 µg strength. The composition of the 100 and 200 µg strengths are dose proportional to the 300 µg strength since they apply to the following condition stated by the guideline: "the amount of the active substance(s) is less than 5% of the tablet core weight, and of the weight of the capsule content."
- *In vitro* dissolution data were submitted that confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Therefore, a biowaiver for the 100, 200, 400, 600 and 800 µg tablet strengths has been granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (both male and female), aged 18-46 years. Each subject received a single dose (300 µg; 1 x 300 µg sublingual tablet) of one of the two fentanyl formulations. Subjects had to wet the mouth by swallowing 20 ml of water before placing the tablet under the tongue at the deepest part. The sublingual tablets could not be swallowed, but were allowed to completely dissolve in the sublingual cavity without chewing or sucking. Fluid intake was not allowed one hour before and until three hours after drug administration. No food intake was allowed for at least five hours post-dose. There were two dosing periods, separated by a washout period of seven days.

During each treatment period, subjects received a total of three oral doses of naltrexone 50 mg (an opioid antagonist) at the following time points: in the evening of day zero (approximately 12 hours before study medication administration) and on day one (approximately 30 minutes before study medication administration and at 12 hours after administration). This was in accordance with the Draft Guidance on Fentanyl Citrate (Food and Drug Administration). Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors, decreasing the adverse events of fentanyl.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 32 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved. As such, the fasting condition applied in the study is considered adequate. Wetting the mouth before placing the tablet is also acceptable.

The justification for the use of the 300 µg tablets strength is explained above. Although higher doses may be administered to healthy volunteers, safety precautions may be an appropriate reason to apply a lower dose in a bioequivalence study. Moreover, this may be also an ethical issue, depending on the ethical committee in a specific country. The single dose bioequivalence study with the 300 µg tablet strength to support the application was considered sufficient.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fentanyl citrate under fasted conditions.

Treatment N=36	**AUC_{0-t} (pg.h/ml)**	**$AUC_{0-\infty}$ (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	3358 ± 1631	4058 ± 2356	641 ± 209	1.0 (0.33 – 2.5)	15.2 ± 11.6
Reference	3399 ± 1658	3982 ± 2202	664 ± 213	1.0 (0.33 – 2.0)	13.6 ± 5.8
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	-	0.97 (0.90 – 1.05)	-	-
CV (%)	12.3	-	19.1	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Submena 300 µg is considered bioequivalent with Abstral 300 µg.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Submena.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Respiratory depression • Local tolerability • Misuse • Medication errors • Drug dependence • Drug abuse • Off-label use • Drug diversion • Overdose
Important potential risks	• Brain lesion • Cardiovascular depression • Accidental exposure • Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs
Missing information	• Limited information on use in children and adolescents • Limited use in women who are pregnant or breast-feeding women • Limited use in patients who have heart, kidney or liver problems • Limited information on long-term use of fentanyl

Next to routine pharmacovigilance activities, additional risk minimisation measures, including educational material, have been agreed pursuant to Article 21a or 22 of Directive 2001/83/EC. Prior to launch, in each member state the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material with the National Competent Authority including communication media, distribution modalities, and any other aspects of the program, with the national competent authority.

The educational materials is aimed at increasing awareness about the important risks associated with fentanyl treatment and providing guidance on how to manage the associated risks. The educational material includes a healthcare professional guide and a patient/carer guide.

The MAH shall ensure that in each member state where fentanyl is marketed, all physicians, pharmacists and patients expected to prescribe/dispense/use fentanyl are provided with educational material regarding the correct and safe use of the product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Abstral. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the 300 microgram product is similar to the pharmacokinetic profile of the respective reference product strength. A biowaiver has been granted for the additional product strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Abstral (SE/H/0575/004). The PL is in line, with exception of some minor product particular sections. For the lay-out, the MAH refers to the lay-out of Methadone hydrochloride GL 5 mg, 10 mg, 20 mg, 40 mg and 60 mg tablets (DK/H/2990/001-005). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Submena 100, 200, 300, 400, 600 and 800 microgram, tablets for sublingual use have a proven chemical-pharmaceutical quality and are generic forms of Abstral 100, 200, 300, 400, 600 and 800 microgram, tablets for sublingual use. Abstral are well-known medicinal products with established favourable efficacy and safety profiles. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Submena with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 August 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse