COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fentanyl Aurobindo 100 microgram, 200 microgram, 400 microgram, 600 microgram and 800 microgram, buccal tablets (fentanyl citrate)

NL/H/6206/001-005/DC

Date: 9 July 2024

This module reflects the scientific discussion for the approval of Fentanyl Aurobindo 100 microgram, 200 microgram, 400 microgram, 600 microgram and 800 microgram, buccal tablets. The procedure was finalised at 22 August 2019 in Austria (AT/H/0930/001-005). After a transfer on 7 May 2024, the current RMS is the Netherlands. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Fentanyl Aurobindo 100 microgram, 200 microgram, 400 microgram, 600 microgram and 800 microgram, buccal tablets from Aurobindo Pharma Limited.

The product is indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.
BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.
Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

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

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

Fentanyl is an opioid analgesic, interacting predominantly with the opioid μ-receptor. Its primary therapeutic actions are analgesia and sedation. Secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

Conditions pursuant to Article 21a of Directive 2001/83/EC have been agreed. For more details please refer to section VI of this assessment report.

The concerned member states (CMS) involved in this procedure were France and Poland.

II. QUALITY ASPECTS

II.1 Introduction

Fentanyl Aurobindo is a buccal tablet which is presented in an aluminium laminated blister pack made of PVC/aluminium foil/polyamide/PVC with paper/polyester cover foil.

II.2 Drug Substance

The active substance in Fentanyl Aurobindo is fentanyl citrate. The specification of the active substance meets the current scientific requirements.

Quality control of drug substance
The adequate quality of the active substance has been shown by submitting the appropriate control data.

Stability of drug substance
The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Fentanyl Aurobindo contains the following excipients:
Each tablet contains 67,1 mg sorbitol, Mannitol,Citric acid anhydrous, Macrogol, L-Arginine, Magnesium stearate.

Pharmaceutical development
The development of the product has been sufficiently made and deemed appropriate.

Manufacturing process
The release specification includes the check of all parameters relevant to this pharmaceutical form.
The packaging of the medicinal product complies with the current legal requirements.

Control of excipients
The usage of all the excipients has been described.

Quality control of drug product
Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The pharmaceutical quality of Fentantyl Aurobindo has been adequately shown.

Stability of drug product
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 18 months when stored below 30°C and stored in the original package to protect from moisture.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fentanyl Aurobindo buccal tablet is 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

Pharmacodynamic, pharmacokinetic and toxicological properties of fentanyl are well known. As fentanyl citrate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic product; therefore, new clinical studies are generally neither required nor submitted.
The dossier contains an adequate review of published literature concerning aspects of pharmacology, pharmacodynamics, efficacy and safety of fentanyl citrate.

IV.2 Pharmacokinetics

The pharmacokinetic properties of fentanyl citrate are well established.

The applicant carried out the BE study only with the 800 µg strength and waived additional strengths based on dissolution data only.

Bioequivalence studies
Single center, randomized, single dose, laboratory-blinded, 4-period, 2-sequence, full replicate crossover study. The objective of this study was to determine the bioequivalence of two different formulations of fentanyl after a single buccal dose administration under fasting conditions.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h
Test	11374.4	12175.9	1393.3	1.67 (0.67-6.00)
Reference	10337.4	11020.7	1345.6	1.67 (0.67-6.00)
***Ratio (90% CI)**	112.42 (106.33-118.85)		105.82 (97.76 114.55)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max} Maximum plasma concentration

t_{max} Time until Cmax is reached

*ln-transformed values

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Fentanyl Aurobindo 800 µg buccal tablet is considered bioequivalent with Effentora 800 Mikrogramm buccal tablet from Teva B.V..

The biowaiver based on dissolution data for additional strengths is acceptable.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: analgesics; opioids; ATC code N02AB03.

Abundant data on fentanyl 's clinical pharmacodynamics are available in the public literature. The applicant has not provided additional studies and further studies are not required.

IV.4 Clinical efficacy/Clinical safety

The indications claimed are in accordance with those of the reference product Effentora 800 Mikrogramm buccal tablet from Teva B.V..

The efficacy of fentanyl is established and documented in controlled clinical studies. No new efficacy or safety data have been submitted and none are required for this generic application.

IV.5 Risk Management Plan and Summary of the Pharmacovigilance System Master File

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 Fentanyl Aurobindo buccal tablets.

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

Important identified risks	Drug abuse Drug diversion Pharmacodependence Drug misuse • Incorrect/no titration Off-label use including: • Use in cancer patients who are not already receiving opioid maintenance therapy for chronic cancer pain • Use in non-cancer acute or chronic pain Medication errors Overdose Respiratory depression Local tolerability
Important potential risks	Cardiovascular/Circulatory depression Anaphylaxis Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis following repeated application of high doses of fentanyl in rats (relevance to human is unknown) Drug interaction with serotonergic drugs leading to serotonin syndrome Accidental exposure
Missing information	Pregnant, breastfeeding women Paediatric population Patients with renal or hepatic dysfunction Long-term use

Table 3. Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Drug abuse	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.6. SmPC section 4.2 and 4.4 where advice is given to HCP on monitoring the abuse potential.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription.	Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Drug diversion	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.6. SmPC section 4.2 and 4.4 where advice is given to HCP on monitoring the abuse potential. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Pharmacodependence	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.6. SmPC section 4.2 and 4.4 where advice is given to HCP on monitoring the abuse potential. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Drug misuse - Incorrect/no titration	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2 and 4.4.	Healthcare Professional Guide • Opioid prescribing guide

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	SmPC section 4.4 where advice is given to HCP on monitoring the during the titration process. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	• Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Off-label use – Use in cancer patients who are not already receiving opioid maintenance therapy for chronic cancer pain – Use in non-cancer acute or chronic pain	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2 and 4.4. SmPC section 4.4 where advice is given to HCP on monitoring the during the titration process. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Medication Error	**Routine risk minimisation measures:** SmPC sections 4.2 and 4.9 **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Overdose	**Routine risk minimisation measures:** SmPC sections 4.2 and 4.9 **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Respiratory depression	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7 and 4.9. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide • Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Local tolerability	**Routine risk minimisation measures:** SmPC sections 4.3 and 4.8 **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription	None
Important Potential Risks		
Cardiovascular / Circulatory depression	**Routine risk communication:** SmPC sections 4.4 and 4.8.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	SmPC section 4.4 where advice is given to HCP on monitoring the opioid-related undesirable effects **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	
Anaphylaxis	**Routine risk communication:** SmPC sections 4.4 and 4.8. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None
Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis following repeated application of high doses of fentanyl in rats (relevance to human is unknown)	**Routine risk communication:** SmPC sections 5.3. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None
Drug interaction with serotonergic drugs leading to serotonin syndrome	**Routine risk communication:** SmPC sections 4.4 and 4.8. SmPC section 4.4 where advice is given to HCP on monitoring the opioid-related undesirable effects **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None
Accidental exposure	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2, 4.4, 4.9 and 6.6. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	Healthcare Professional Guide • Opioid prescribing guide • Brochure on breakthrough pain • Fentanyl prescribing guide • Titration guide tool Patient guide

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		• Document explaining the titration process and dosing • Daily Pain Journal to record daily pain levels • Question and answer document
Missing Information		
Pregnant, breastfeeding women	**Routine risk communication:** SmPC sections 4.6 and 4.8. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None
Paediatric population	**Routine risk communication:** SmPC sections 4.2, 4.4 and 4.9. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None
Patients with renal or hepatic dysfunction	**Routine risk communication:** SmPC sections 4.2, 4.4 and 5.2 SmPC section 4.4 where advice is given to HCP on monitoring renal function during the titration process. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None
Long-term use	**Routine risk communication:** SmPC section 6. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.	None

Summary of the Pharmacovigilance System Master File

The applicant submitted the summary of the pharmacovigilance system in the scope of this procedure.

The summary includes the following elements:

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance
- The Member States in which the qualified person resides and carries out his/her tasks
- The contact details of the qualified person
- A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC
- A reference to the location where the pharmacovigilance system master file for the medicinal product is kept

IV.6 Discussion on the clinical aspects

The dossier contains an adequate review of published clinical data and bioequivalence has been shown.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Spanish.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

In each Member State where Fentanyl Aurobindo is marketed the Applicant shall agree an updated educational programme with the National Competent Authority. The Applicant shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Fentanyl Aurobindo is marketed all healthcare professionals who are expected to prescribe Fentanyl Aurobindo are provided with an information pack.

The pharmaceutical quality of Fentanyl Aurobindo has been adequately shown, and no new non-clinical or clinical concerns have been identified.

The benefit/risk relation is considered positive.

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
NL/H/6206/1-5/IA/013	C.I.3. a) Implementation of wording agreed by the competent authority	Yes	13 June 2024	Approved	N.A.