Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Fluoxetine 10 mg hard capsules
Fluoxetine 20 mg hard capsules
Fluoxetine 30 mg hard capsules
Fluoxetine 40 mg hard capsules
Fluoxetine 60 mg hard capsules

fluoxetine hydrochloride

PL 25298/0300-4

Brown & Burk UK Ltd

LAY SUMMARY

Fluoxetine 10 mg hard capsules
Fluoxetine 20 mg hard capsules
Fluoxetine 30 mg hard capsules
Fluoxetine 40 mg hard capsules
Fluoxetine 60 mg hard capsules
fluoxetine hydrochloride

This is a summary of the Public Assessment Report (PAR) for Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules and what are they used for?
The application for Fluoxetine 20 mg hard capsules is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Prozac 20 mg hard capsules.

The applications for Fluoxetine 10 mg, 30 mg, 40 mg and 60 mg hard capsules are for hybrid medicines. This means that the medicines are similar to a reference medicine already authorised, called Prozac 20 mg hard capsules, albeit with certain differences. In this case Fluoxetine 10 mg, 30 mg, 40 mg and 60 mg hard capsules are a different strength to the reference product.

These medicines are used to treat the following conditions:
Adults:

- Major depressive episodes
- Obsessive-compulsive disorder
- Bulimia nervosa: Fluoxetine is used alongside psychotherapy for the reduction of
- binge-eating and purging.

Children and adolescents aged 8 years and above:

- Moderate to severe major depressive disorder, if the depression does not respond to psychological therapy after 4-6 sessions. Fluoxetine should be offered to a child or young person with moderate to severe major depressive disorder only in combination with psychological therapy.

How do Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules work?
Fluoxetine hard capsules contain the active ingredient fluoxetine (as fluoxetine hydrochloride), which belongs to a group of medicines called selective serotonin re-uptake inhibitor (SSRI) antidepressants.

Everyone has a substance called serotonin in their brain. People who are depressed or have obsessive compulsive disorder or bulimia nervosa have lower levels of serotonin than others.

It is not fully understood how fluoxetine and other SSRIs work, but they may help by increasing the level of serotonin in the brain.

How are Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules used?
The pharmaceutical form of these medicines is a hard capsule and the route of administration is oral (by mouth).

The recommended dose in adults is:
- Depression:

The recommended dose is 20 mg daily. The patient's doctor will review and adjust their patient's dosage if necessary within 3 to 4 weeks of the start of treatment. If required, the dosage can be gradually increased up to a maximum of 60 mg daily. The dose should be increased carefully to ensure that the patient receives the lowest effective dose. The patient may not feel better immediately when they first start taking their medicine for depression. This is usual because an improvement in depressive symptoms may not occur until after the first few weeks. Patients with depression should be treated for at least 6 months.

- Bulimia nervosa:

The recommended dose is 60 mg daily.

- Obsessive compulsive disorder:

The recommended dose is 20 mg daily. The patient's doctor will review and adjust the patient's dosage if necessary after 2 weeks of treatment. If required, the dosage can be gradually increased up to a maximum of 60 mg daily. If no improvement is noted within 10 weeks, the doctor will reconsider their patient's treatment.

Use in children and adolescents aged 8 to 18 years with depression:
Treatment should be started and be supervised by a specialist. The starting dose is 10 mg/day (often given as a liquid formulation of fluoxetine). After 1 to 2 weeks, the patient's doctor may increase the dose to 20 mg/day. The dose should be increased carefully to ensure that the patient receives the lowest effective dose. Lower weight children may need lower doses. If there is a satisfactory response to treatment, the patient's doctor will review the need for continuing treatment beyond 6 months. If the patient has not improved within 9 weeks, the patient's doctor will reassess their treatment.

Use in the elderly:
The patient's doctor will increase the dose with more caution and the daily dose should generally not exceed 40 mg. The maximum dose is 60 mg daily.

Use in patients with liver impairment:
If the patient has a liver problem or are using other medication that might affect fluoxetine, their doctor may decide to prescribe a lower dose or tell them to use fluoxetine every other day.

For further information on how Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules have been shown in studies?
Because Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules are generic or hybrid medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules are generic or hybrid medicines and are bioequivalent to the reference medicine, their benefits and possible side effects are considered to be the same as the reference medicine.

Why were Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules approved?
It was concluded that, Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules have been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules. The RMP details the important risks of Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules, how these risks can be minimised, any uncertainties about Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules (missing information), and how more information will be obtained about the important risks and uncertainties.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules

Marketing authorisations for Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules were granted in the United Kingdom (UK) on 28 September 2022.

The full PAR for Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules follows this summary.

This summary was last updated in November 2022.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules (PL 25298/0300-4) could be approved.

The products are approved for the following indications:
Adults:
Major depressive episodes.
Obsessive-compulsive disorder.
Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.
Children and adolescents aged 8 years and above:
Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α1-, α2, and β-adrenergic serotonergic; dopaminergic; histaminergic1; muscarinic; and GABA receptors.

The application for Fluoxetine 20 mg hard capsules was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Prozac 20 mg hard capsules, that has been licensed for a suitable time, in line with the legal requirements.

The applications for Fluoxetine 10 mg, 30 mg, 40 mg and 60 mg hard capsules were approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be hybrid medicinal products of a suitable originator product, Prozac 20 mg hard capsules, that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic/hybrid medicinal products of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic/hybrid medicinal products of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations for Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules were granted in the United Kingdom (UK) on 28 September 2022.

II QUALITY ASPECTS

II.1 Introduction

These products consist of hard capsules containing 10 mg, 20 mg, 30 mg, 40 mg or 60 mg of fluoxetine (as hydrochloride).

In addition to fluoxetine hydrochloride, these products also contain the following excipients:
Capsules content:
Pregelatinized starch (Vegetable origin)
Iron oxide yellow (E 172)
Titanium dioxide (E 171)
Gelatin
Sodium lauryl sulphate
Brilliant blue FCF (E 133) (10 mg)
Patent Blue V (E 131) (20 mg, 30 mg, 60 mg)
Iron oxide red (E 172) (40 mg)
FD&C Blue 1 (E 133) (40 mg)

Printing ink:
Shellac (E904)
Dehydrated alcohol (E1510)
Isopropyl alcohol
Butyl alcohol
Propylene glycol (E1520)
Strong ammonia solution (E527)
Black iron oxide (E172)
Potassium hydroxide (E525)

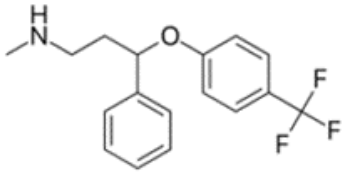
The finished products are packaged in aluminium-clear/transparent PVC/PVdC blister packs in a pack size of 2, 5, 7, 10, 12, 14, 20, 28, 30, 42, 50, 56, 60, 70, 90, 98, 100 and 500 capsules. Not all pack sizes may be marketed.

Fluoxetine 20 mg hard capsules are also available in white/opaque HDPE bottle packs of 1000 capsules with polypropylene screw caps.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN:	**Fluoxetine Hydrochloride**
Chemical Name:	Benzenepropanamine,N-methyl-γ-[4-(trifluoromethyl)phenoxy]-hydrochloride, (±). or (±)–N-Methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy]propylamine, hydrochloride or (3RS)-N-Methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propan-1-amine, hydrochloride
Molecular Formula:	$C_{17}H_{19}ClF_3NO$
Chemical Structure:	



and enantiomer •HCl

Molecular Weight:	345.79
Appearance:	White or almost white, crystalline powder.
Solubility:	Sparingly soluble in water and in methylene chloride, freely soluble in methanol.

Fluoxetine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, no excipients of animal or human origin are used in the final products. Satisfactory TSE declarations have been provided by the manufacturers.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions ‘Do not store above 25ºC. Store in the original package’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of fluoxetine hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic/hybrid versions of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of fluoxetine hydrochloride are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following Bioequivalence study.

This study was an open label, randomised, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, truncated oral bioequivalence study comparing the test product Fluoxetine 60 mg hard capsules, versus the reference product, Prozac 20 mg hard capsules (3 x 20 mg capsules) in healthy, adult, human subjects, under fasting conditions.

Subjects were administered test (1 x 60 mg capsule) or reference product (3 x 20 mg capsules), after a fast of at least 10 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 35 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Interval	CV%
C_{max}(ng/mL)	97.50	94.90-100.18	7.57
AUC_{0-72}(ng.hr/mL)	95.59	93.37-97.87	6.49

ANOVA p-values

P-Value	PK Parameter	
	C_{max} (ng/mL)	AUC_{0-72} (ng.hr/mL)
Sequence	0.2148	0.2406
Period	0.2459	*0.0198
Treatment	0.1245	*0.0025

* Statistically significant at 5% level of significance

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths (10 mg, 20 mg, 30 mg and 40 mg) of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 60 mg product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Prozac 20 mg hard capsules (FR/H/0242/002) for text and key safety messages and Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (PL 25298/0160-0163) for the format, design, and layout. The bridging report submitted by the applicant is acceptable.

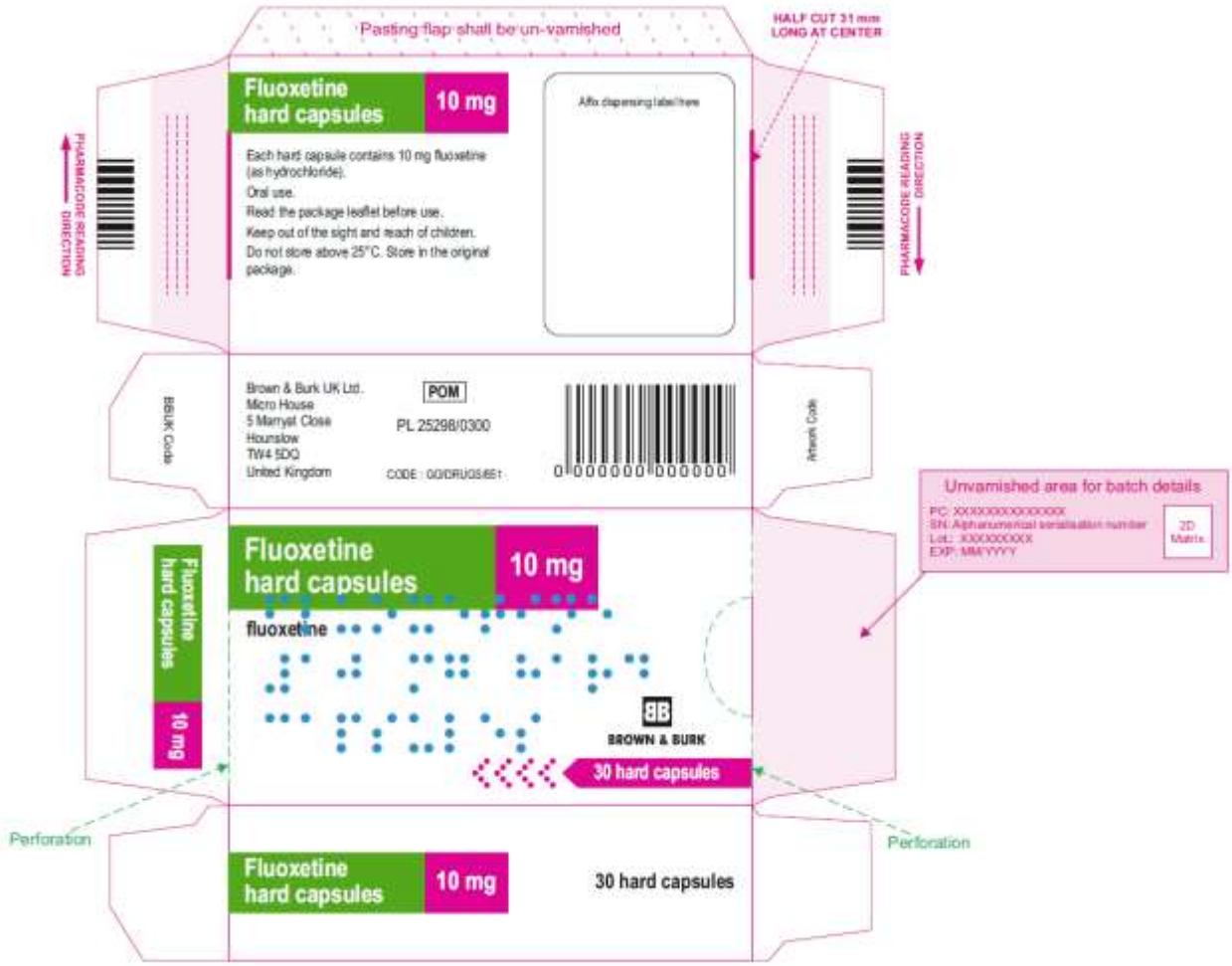
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fluoxetine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

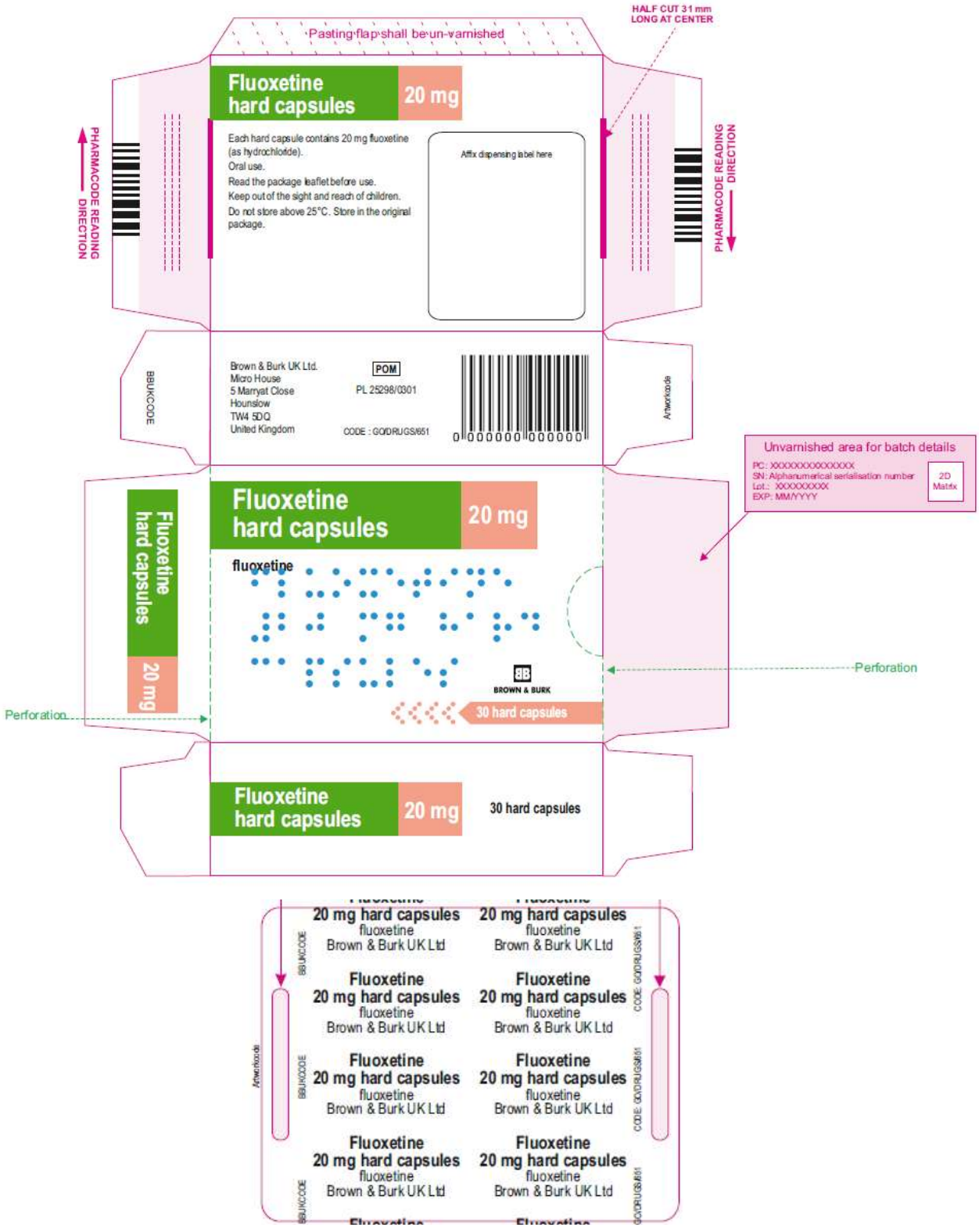
The Summaries of Product Characteristics (SmPCs) Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Pasting flap shall be un-varnished
HALF CUT 31 mm LONG AT CENTER
Fluoxetine hard capsules
10 mg
Each hard capsule contains 10 mg fluoxetine (as hydrochloride).
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package.
Affix dispensing label here
PHARMACODE READING DIRECTION
Brown & Burk UK Ltd.
Micro House
5 Marryat Close
Hounslow
TW4 5DQ
United Kingdom
POM
PL 25298/0300
CODE : GO/DRUGS/651
BB/UK Code
Artwork Code
Unvarnished area for batch details
PC: XXXXXXXXXXXXX
SN: Alphanumerical serialisation number
Lot: XXXXXXXXX
EXP: MM/YYYY
2D Matrix
fluoxetine
BROWN & BURK
30 hard capsules
Perforation
Perforation
30 hard capsules


fluoxetine
Brown & Burk UK Ltd
Fluoxetine
10 mg hard capsules
BB/UK CODE
CODE: GO/DRUGS/651


Pasting flap shall be un-varnished
HALF CUT 31 mm LONG AT CENTER
Fluoxetine hard capsules
20 mg
Each hard capsule contains 20 mg fluoxetine (as hydrochloride).
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package.
Affix dispensing label here
PHARMACODE READING DIRECTION
Brown & Burk UK Ltd.
Micro House
5 Marryat Close
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TW4 5DQ
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POM
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CODE : GO/DRUGS/651
BBUKCODE
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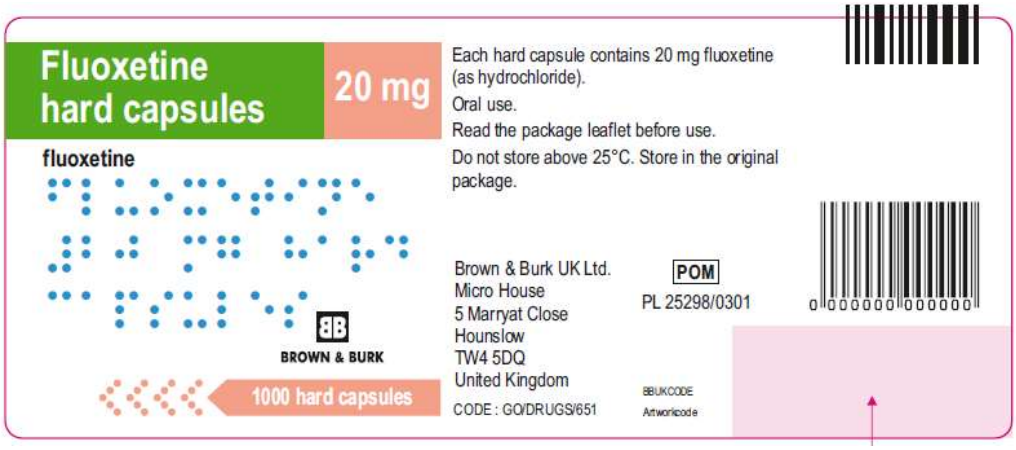
EXP: MM/YYYY
2D Matrix
fluoxetine
BROWN & BURK
30 hard capsules
Perforation
20 mg hard capsules
fluoxetine
Brown & Burk UK Ltd


Fluoxetine
hard capsules
20 mg
fluoxetine
BROWN & BURK
1000 hard capsules
Each hard capsule contains 20 mg fluoxetine (as hydrochloride).
Oral use.
Read the package leaflet before use.
Do not store above 25°C. Store in the original package.
Brown & Burk UK Ltd.
Micro House
5 Marryat Close
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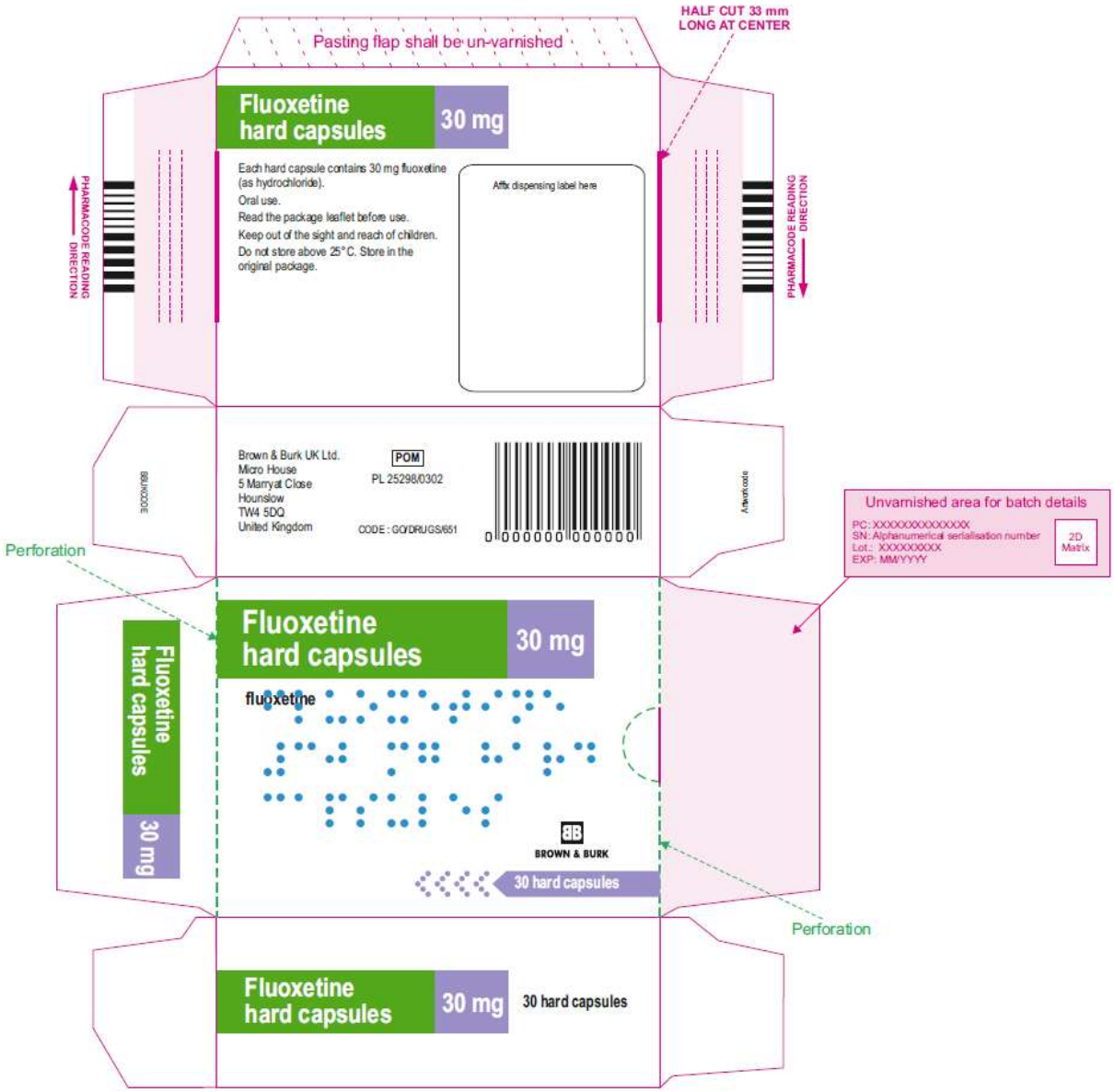
CODE : GO/DRUGS/651
POM
PL 25298/0301
BBUKCODE
Artworkcode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HALF CUT 33 mm LONG AT CENTER
Fluoxetine hard capsules
30 mg
Each hard capsule contains 30 mg fluoxetine (as hydrochloride).
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package.
Affix dispensing label here
PHARMACODE READING DIRECTION
Brown & Burk UK Ltd.
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5 Marryat Close
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TW4 5DQ
United Kingdom
POM
PL 25298/0302
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PC: XXXXXXXXXXXXX
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2D Matrix
Perforation
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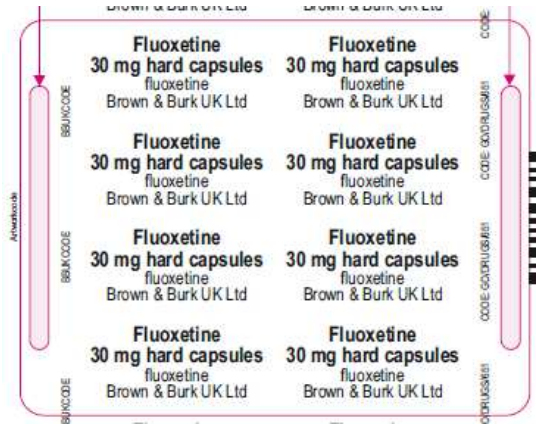
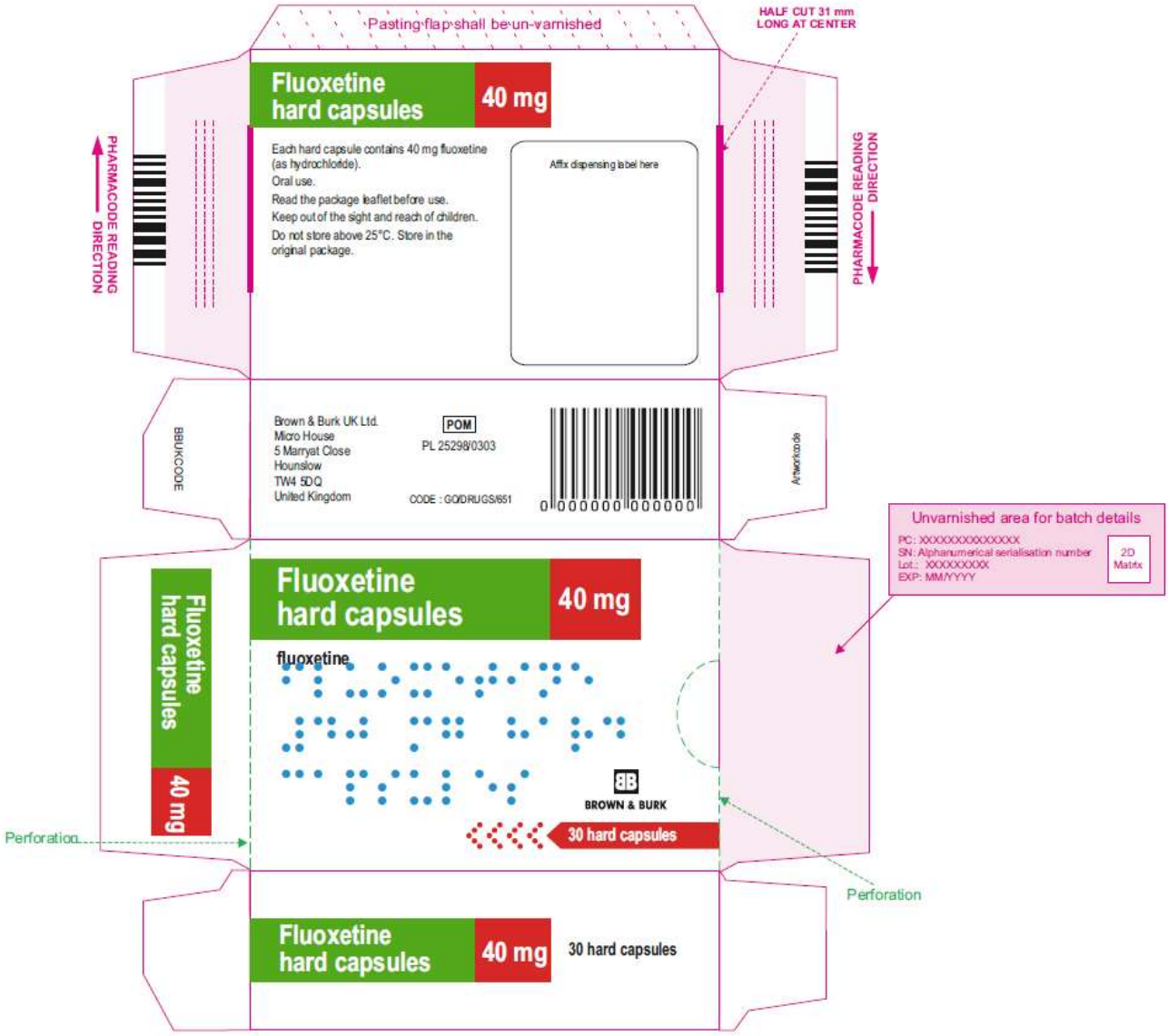
BROWN & BURK
30 hard capsules
Perforation
Fluoxetine hard capsules
30 mg
30 hard capsules


Fluoxetine
30 mg hard capsules
fluoxetine
Brown & Burk UK Ltd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HALF CUT 31 mm LONG AT CENTER
Fluoxetine hard capsules
40 mg
Each hard capsule contains 40 mg fluoxetine (as hydrochloride).
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package.
Affix dispensing label here
PHARMACODE READING DIRECTION
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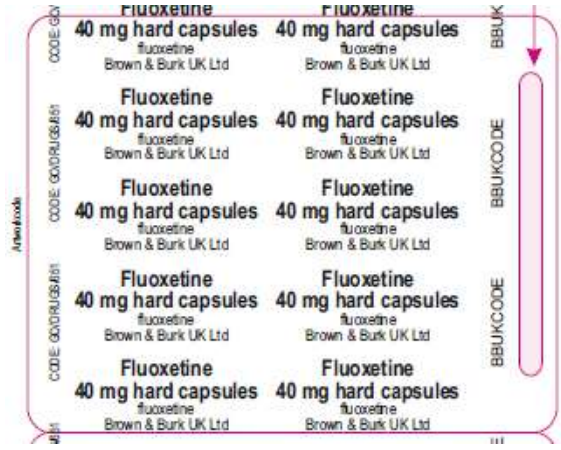
2D Matrix
Fluoxetine hard capsules
40 mg
fluoxetine
BROWN & BURK
30 hard capsules
Perforation
Perforation
Fluoxetine hard capsules
40 mg
30 hard capsules


Fluoxetine
40 mg hard capsules
fluoxetine
Brown & Burk UK Ltd
BBUKCODE
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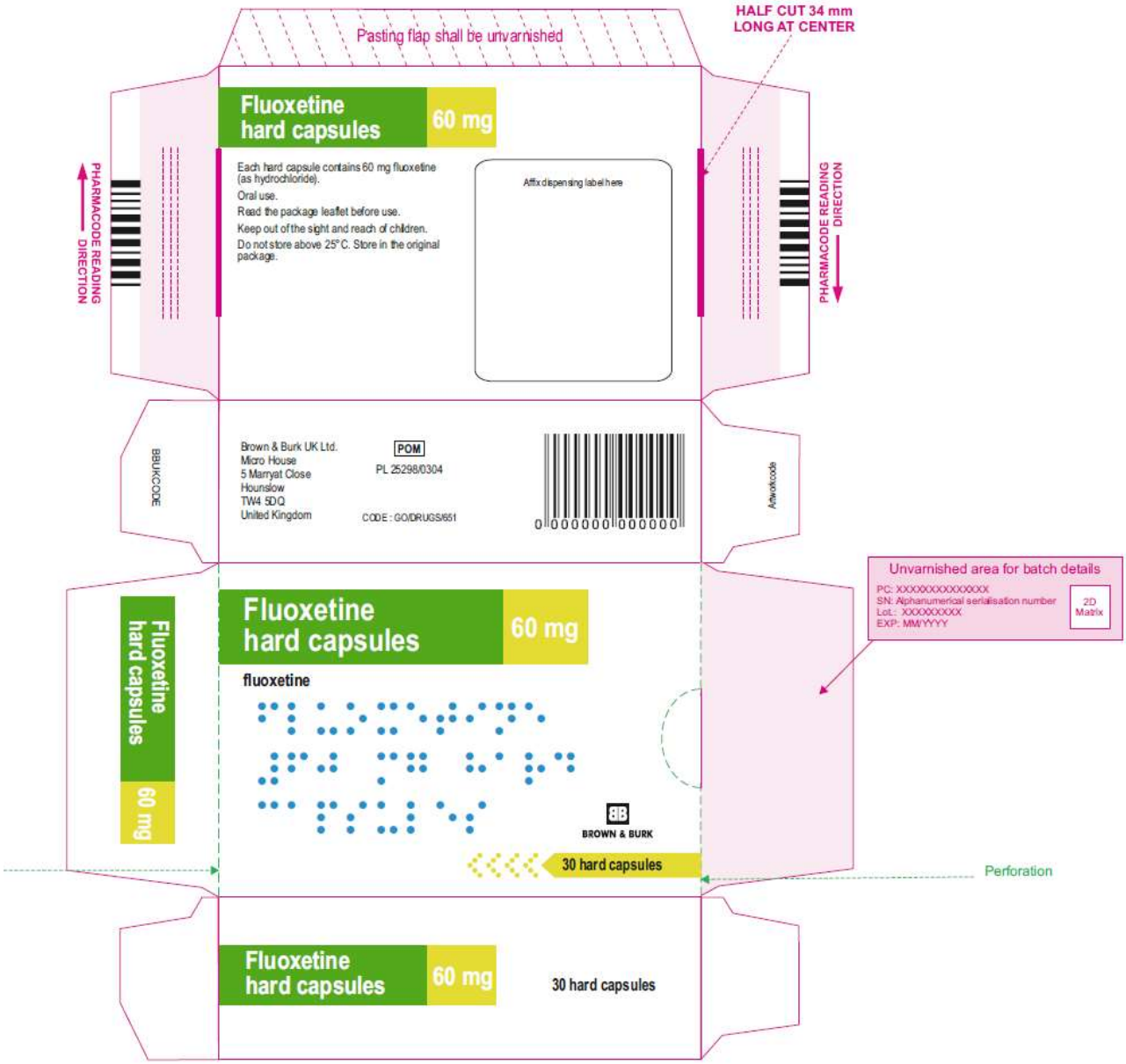
Pasting flap shall be unvarnished
HALF CUT 34 mm LONG AT CENTER
Fluoxetine hard capsules
60 mg
Each hard capsule contains 60 mg fluoxetine (as hydrochloride).
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package.
Affix dispensing label here
PHARMACODE READING DIRECTION
Brown & Burk UK Ltd.
Micro House
5 Marryat Close
Hounslow
TW4 5DQ
United Kingdom
POM
PL 25298/0304
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BROWN & BURK
30 hard capsules
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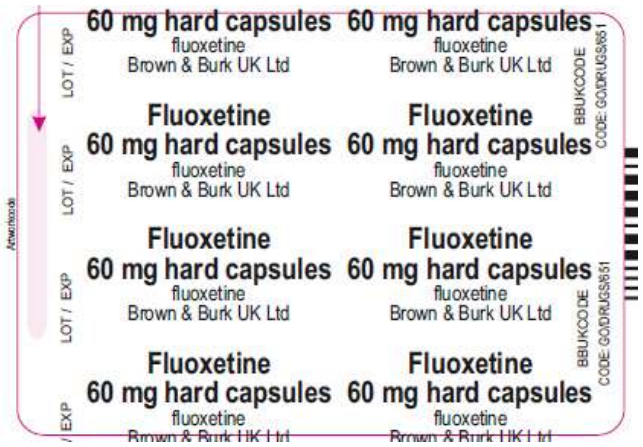
60 mg hard capsules
fluoxetine
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Fluoxetine
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CODE: GO/DRUGS/651
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TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**