

Fexofenadine Hydrochloride 120 mg Film-coated Tablets

Fexofenadine Hydrochloride 180 mg Film-coated Tablets

PL 36390/0053-4

UKPAR

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Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets

PL 36390/0053-4

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted STD Chemicals Limited Marketing Authorisations (licences) for the medicinal products Fexofenadine Hydrochloride 120 mg and 180 mg Film-coated Tablets (PL 36390/0053-4) on 19th September 2011. These are prescription-only medicines (POM).

The active ingredient, fexofenadine hydrochloride, belongs to a group of medicines called antihistamines.

Fexofenadine Hydrochloride 120 mg Film-coated Tablets are used to relieve the symptoms of hay fever (seasonal allergic rhinitis), such as sneezing, itchy and runny nose and red, itchy and watery eyes.

Fexofenadine Hydrochloride 180 mg Film-coated Tablets are used to relieve the symptoms of long-term skin reactions (chronic idiopathic urticaria), such as itching, swelling and rashes.

Fexofenadine Hydrochloride 120 mg and 180 mg Film-coated Tablets are not suitable for children under 12 years of age.

These applications are considered to be identical to the previously granted licences for Fexofenadine Hydrochloride 120 mg and 180 mg Film-coated Tablets (PL 08137/0121-2), authorised to Neolab Limited on 25th March 2011.

No new or unexpected safety concerns arose from these simple applications. It was judged that the benefits of Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets outweigh the risk; hence Marketing Authorisations have been granted.

Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets

PL 36390/0053-4

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted STD Chemicals Limited Marketing Authorisations for the medicinal products Fexofenadine Hydrochloride 120 mg and 180 mg Film-coated Tablets (PL 36390/0053-4) on 19th September 2011. The products are prescription-only medicines.

These are simple, abridged, 'informed consent' applications, submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisations for Fexofenadine Hydrochloride 120 mg and 180 mg Film-coated Tablets (PL 08137/0121-2), authorised to Neolab Limited on 25th March 2011 through incoming Mutual Recognition procedures [IE/H/0230/001-2/MR] where Ireland was the Reference Member State (RMS).

Fexofenadine Hydrochloride 120 mg Film-coated Tablets are indicated in adults and children aged 12 years and over for the relief of symptoms associated with seasonal allergic rhinitis.

Fexofenadine Hydrochloride 180 mg Film-coated Tablets are indicated in adults and children aged 12 years and over for the relief of symptoms associated with chronic idiopathic urticaria.

Fexofenadine hydrochloride is a non-sedating H₁ antihistamine (ATC code: RO6A X26). It is a pharmacologically active metabolite of terfenadine. Human histamine wheal and flare studies following single and twice daily doses of fexofenadine hydrochloride demonstrate that the drug exhibits an antihistaminic effect beginning within one hour, achieving maximum at 6 hours and lasting 24 hours. There is no evidence of tolerance to these effects after 28 days of dosing. A positive dose-response relationship between doses of 10mg to 130mg taken orally was found to exist. In this model of antihistaminic activity, it was found that doses of at least 130mg were required to achieve a consistent effect that was maintained over a 24 hour period. Maximum inhibition in skin wheal and flare areas was greater than 80%. Clinical studies conducted in seasonal allergic rhinitis have shown that a dose of 120mg is sufficient for 24 hour efficacy.

The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for products that are identical to already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). It is not considered that these medicinal products represent any risk to the environment. There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The availability of these medicinal products, which are identical to the cited reference products, will not lead to any increase in environmental exposure concentrations of the active ingredient.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.

PHARMACEUTICAL ASSESSMENT

LICENCE NUMBERS:	PL 36390/0053-4
PROPRIETARY NAME:	Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets
ACTIVE INGREDIENTS:	Fexofenadine hydrochloride
COMPANY NAME:	STD Chemicals Ltd
E.C. ARTICLE:	Article 10(c) of Directive 2001/83/EC (as amended)
LEGAL STATUS:	POM

1. INTRODUCTION

These are simple abridged applications, submitted under Article 10(c) of Directive 2001/83/EC (as amended) for Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets. The proposed MAH is STD Chemicals Ltd.

The reference products are Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets (PL 08137/0121-2), authorised to Neolab Limited on 25th March 2011 through incoming Mutual Recognition procedures [IE/H/0230/001-2/MR] where Ireland was the Reference Member State (RMS). The proposed and reference products are considered identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The approved names of the products are Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets. The products have been named in line with current requirements and the product names are acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each film-coated tablet contains 120 mg or 180 mg of the active ingredient fexofenadine hydrochloride, equivalent to 112 mg and 168 mg of fexofenadine respectively. The tablets are licensed for marketing in polyvinylchloride (PVC) / polyvinylidene chloride (PVdC) / aluminium foil blister strips, which are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons, in pack sizes of 7, 10, 15, 20, 30, 50, 100 or 500 film-coated tablets. The MAH has stated that not all pack sizes may be marketed. The container closure systems and pack sizes are identical to those for the reference products.

The approved shelf-life (3 years) and storage conditions ('Store the tablets in the original package. This medicinal product does not require any special temperature storage conditions') are identical to the details registered for the reference products.

2.3 Legal status

POM - The products are available subject to a medical prescription.

2.4 Marketing Authorisation Holder / Contact Persons/Company

The proposed Marketing Authorisation Holder is 'STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW'.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product / shelf-life specification

The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specifications are in line with the details registered for the cross-reference products.

2.10 TSE Compliance

The only excipient used that contains material of animal or human origin is magnesium stearate. Satisfactory documentation has been provided by the magnesium stearate supplier stating that the magnesium stearate they provide complies with the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'. None of the excipients are sourced from genetically modified organisms.

3. EXPERT REPORT

A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The 120 mg strength tablets are peach-coloured, oblong, biconvex, film coated tablets. The 180 mg strength tablets are yellow-coloured, oblong, biconvex, film coated tablets, plain on one side and with a central breakline on the reverse side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The appearance of the products is identical to that of the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) / LABELLING

PIL

The approved PIL is satisfactory and in line with the approved SmPCs. It has been prepared according to the Quality Review of Documents (QRD) template and is consistent with the details registered for the cross-reference products.

PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for the reference products, Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets (PL 08137/0121-2). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference products. The bridging is accepted.

Labelling

Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for currently unmarketed pack sizes to the MHRA for approval before those packs are commercially marketed.

7. CONCLUSIONS

The grounds for these applications are considered adequate. Marketing Authorisations were therefore granted.

NON-CLINICAL ASSESSMENT

These are simple, abridged, 'informed consent' applications made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

CLINICAL ASSESSMENT

These are simple, abridged, 'informed consent' applications made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisations for Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets (PL 08137/0121-2; Neolab Limited).

No new clinical data have been supplied with the applications, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

These applications are considered identical to the previously granted licences for Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets (PL 08137/0121-2; Neolab Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs, PIL and labelling are satisfactory and consistent with the details registered for the cross-reference products.

PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for the reference products, Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets (PL 08137/0121-2).

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products. The benefit: risk ratio is considered to be positive.

Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets

PL 36390/0053-4

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation applications on 5th May 2011.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 3rd June 2011.
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 2nd August 2011.
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 15th August 2011.
- 5 The applications were determined on 19th September 2011.

Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets

PL 36390/0053-4

STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Fexofenadine Hydrochloride 120 mg Film-coated Tablets (PL 36390/0053) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fexofenadine Hydrochloride 120 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 120mg of fexofenadine hydrochloride, which is equivalent to 112mg of fexofenadine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Peach coloured, oblong, biconvex, film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of symptoms associated with seasonal allergic rhinitis.

4.2 Posology and method of administration

Adults and children aged 12 years and over

The recommended dose of fexofenadine hydrochloride for adults and children aged 12 years and over is 120 mg once daily taken before a meal.

Fexofenadine is a pharmacologically active metabolite of terfenadine.

Children under 12 years of age

The efficacy and safety of fexofenadine hydrochloride has not been studied in children under 12.

Special risk groups

Studies in special risk groups (elderly, renally or hepatically impaired patients) indicate that it is not necessary to adjust the dose of fexofenadine hydrochloride in these patients.

4.3 Contraindications

In patients with known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

As with most new drugs there is only limited data in the elderly and renally or hepatically impaired patients.

Fexofenadine hydrochloride should be administered with care in these special groups.

Patients with a history of or ongoing cardiovascular disease should be warned that, antihistamines as a drug class, have been associated with the adverse events, tachycardia and palpitations (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Fexofenadine does not undergo hepatic bioformation and therefore will not interact with other drugs through hepatic mechanisms. Coadministration of fexofenadine hydrochloride with erythromycin or ketoconazole has been found to result in a 2-3 times increase in the level of fexofenadine in plasma. The changes were not accompanied by any effects on the QT interval and were not associated with any increase in adverse events compared to the drugs given singly.

Animal studies have shown that the increase in plasma levels of fexofenadine observed after coadministration of erythromycin or ketoconazole, appears to be due to an increase in gastrointestinal absorption and either a decrease in biliary excretion or gastrointestinal secretion, respectively.

No interaction between fexofenadine and omeprazole has been observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride caused a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration of fexofenadine hydrochloride and aluminium and magnesium hydroxide containing antacids.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of fexofenadine hydrochloride in pregnant women.

Limited animal studies do not indicate direct or indirect harmful effects with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development (*see section 5.3*). Fexofenadine hydrochloride should not be used during pregnancy unless clearly necessary.

Lactation

There are no data on the content of human milk after administering fexofenadine hydrochloride. However, when terfenadine was administered to nursing mothers fexofenadine was found to cross into human breast milk. Therefore fexofenadine hydrochloride is not recommended for mothers breast feeding their babies.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and reported adverse events it is unlikely that fexofenadine hydrochloride tablets will produce an effect on the ability to drive or use machines. In objective tests, Fexofenadine has been shown to have no significant effects on central nervous system function. This means that patients may drive or perform tasks that require concentration. However, in order to identify sensitive people who have an unusual reaction to drugs, it is advisable to check the individual response before driving or performing complicated tasks.

4.8 Undesirable effects

In controlled clinical trials in adults the most commonly reported adverse events related to treatment were headache (7.3%), drowsiness (2.3%), nausea (1.5%) and dizziness (1.5%). The incidence of these events observed with fexofenadine was similar to that observed with placebo.

Events related to treatment that have been reported with an incidence of less than 1% include: fatigue, insomnia, nervousness and sleep disorders or paroniria, such as nightmares and tachycardia, palpitations and diarrhoea. In rare cases, rash, urticaria, pruritus, and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnoea, flushing and systemic anaphylaxis have also been reported.

4.9 Overdose

Symptoms of dizziness, drowsiness, fatigue and dry mouth have been reported with overdose of fexofenadine hydrochloride. Single doses up to 800 mg, and doses up to 690 mg twice daily for 1 month, or 240 mg once daily for 1 year have been administered to healthy subjects without the development of clinically significant adverse events. The maximum tolerated dose of fexofenadine hydrochloride has not been established.

Standard measures should be considered to remove any unabsorbed fexofenadine. Symptomatic and supportive treatment is recommended. Haemodialysis does not effectively remove fexofenadine hydrochloride from blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antihistamines for systemic use, ATC code: RO6A X26.

Fexofenadine hydrochloride is a non-sedating H₁antihistamine. Fexofenadine is a pharmacologically active metabolite of terfenadine.

Human histamine wheal and flare studies following single and twice daily doses of fexofenadine hydrochloride demonstrate that the drug exhibits an antihistaminic effect beginning within one hour, achieving maximum at 6 hours and lasting 24 hours. There is no evidence of tolerance to these effects after 28 days of dosing. A positive dose-response relationship between doses of 10mg to 130mg taken orally was found to exist. In this model of antihistaminic activity, it was found that doses of at least 130mg were required to achieve a consistent effect that was maintained over a 24 hour period. Maximum inhibition in skin wheal and flare areas was greater than 80%. Clinical studies conducted in seasonal allergic rhinitis have shown that a dose of 120mg is sufficient for 24 hour efficacy.

No significant differences in QT_c intervals were observed in adult and adolescent patients with seasonal allergic rhinitis, when given fexofenadine hydrochloride up to 240 mg twice daily for 2 weeks when compared to placebo. Also, no significant change in QT_c intervals was observed in healthy adult subjects given fexofenadine hydrochloride up to 60 mg twice daily for 6 months, 400 mg twice daily for 6.5 days and 240 mg once daily for 1 year, when compared to placebo.

Fexofenadine at concentrations 32 times greater than the therapeutic concentration in man had no effect on the delayed rectifier K⁺ channel cloned from human heart.

Fexofenadine hydrochloride (5-10mg/kg per orally) inhibited antigen induced bronchospasm in sensitised guinea pigs and inhibited histamine release at supratherapeutic concentrations (10- 100µM) from peritoneal mast cells.

5.2 Pharmacokinetic properties

Fexofenadine hydrochloride is rapidly absorbed into the body following oral administration, with T_{max} occurring at approximately 1-3 hours post dose. The mean C_{max} value was approximately 427ng/rnl following the administration of a 120mg dose once daily.

Fexofenadine is 60-70% plasma protein bound. Fexofenadine undergoes negligible metabolism (hepatic or non-hepatic), as it was the only major compound identified in urine and faeces of animals and man. The plasma concentration profiles of fexofenadine follow a bi-exponential decline with a terminal elimination half-life ranging from 11 to 15 hours after multiple dosing. The single and multiple dose pharmacokinetics of fexofenadine are linear for oral doses up to 120mg BID. A dose of 240mg BID produced slightly greater than proportional increase (8.8%) in steady state area under the curve, indicating that fexofenadine pharmacokinetics are practically linear at these doses between 40 mg and 240mg taken daily. The major route of elimination is believed to be via biliary excretion while up to 10% of ingested dose is excreted unchanged through the urine.

5.3 Preclinical safety data

Dogs tolerated 450mg/kg administered twice daily for 6 months and showed no toxicity other than occasional emesis. Also, in single dose dog and rodent studies, no treatment-related gross findings were observed following necropsy.

Radiolabelled fexofenadine hydrochloride in tissue distribution studies of the rat indicated that fexofenadine did not cross the blood brain barrier.

Fexofenadine hydrochloride was found to be non-mutagenic in various *in vitro* and *in vivo* mutagenicity tests.

The carcinogenic potential of fexofenadine hydrochloride was assessed using terfenadine studies with supporting pharmacokinetic studies showing fexofenadine hydrochloride exposure (via plasma AUC values). No evidence of carcinogenicity was observed in rats and mice given terfenadine (up to 150mg/kg/day).

In a reproductive toxicity study in mice, fexofenadine hydrochloride did not impair fertility, was not teratogenic and did not impair pre- or postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline Cellulose
Maize Starch
Magnesium Stearate
Croscarmellose Sodium
Povidone

Film-coating:
Hypromellose (E464)
Macrogol (PEG 400)
Macrogol (PEG 4000)
Titanium Dioxide (E171)
Iron Oxide Yellow (E172)
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store the tablets in the original package. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Alu blister packs of 7, 10, 15, 20, 30, 50, 100 or 500 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

STD CHEMICALS LTD,
HILLBROW HOUSE,
HILLBROW ROAD,
ESHER,
SURREY,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 36390/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2011

10 DATE OF REVISION OF THE TEXT

19/09/2011

The UK Summary of Product Characteristics (SmPC) for Fexofenadine Hydrochloride 180 mg Film-coated Tablets (PL 36390/0054) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fexofenadine Hydrochloride 180 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 180mg of fexofenadine hydrochloride, which is equivalent to 168mg of fexofenadine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow coloured, oblong, biconvex, film coated tablets, plain on one side and with a central breakline on the reverse side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of symptoms associated with chronic idiopathic urticaria.

4.2 Posology and method of administration

Adults and children aged 12 years and over

The recommended dose of fexofenadine hydrochloride for adults and children aged 12 years and over is 180 mg once daily taken before a meal.

Fexofenadine is a pharmacologically active metabolite of terfenadine.

Children under 12 years of age

The efficacy and safety of fexofenadine hydrochloride has not been studied in children under 12.

Special risk groups

Studies in special risk groups (elderly, renally or hepatically impaired patients) indicate that it is not necessary to adjust the dose of fexofenadine hydrochloride in these patients.

4.3 Contraindications

In patients with known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

As with most new drugs there is only limited data in the elderly and renally or hepatically impaired patients.

Fexofenadine hydrochloride should be administered with care in these special groups.

Patients with a history of or ongoing cardiovascular disease should be warned that, antihistamines as a drug class, have been associated with the adverse events, tachycardia and palpitations (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Fexofenadine does not undergo hepatic biotransformation and therefore will not interact with other drugs through hepatic mechanisms. Coadministration of fexofenadine hydrochloride with erythromycin or ketoconazole has been found to result in a 2-3 times increase in the level of fexofenadine in plasma. The changes were not accompanied by any

effects on the QT interval and were not associated with any increase in adverse events compared to the drugs given singly.

Animal studies have shown that the increase in plasma levels of fexofenadine observed after coadministration of erythromycin or ketoconazole, appears to be due to an increase in gastrointestinal absorption and either a decrease in biliary excretion or gastrointestinal secretion, respectively.

No interaction between fexofenadine and omeprazole has been observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride caused a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration of fexofenadine hydrochloride and aluminium and magnesium hydroxide containing antacids.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of fexofenadine hydrochloride in pregnant women.

Limited animal studies do not indicate direct or indirect harmful effects with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development (*see section 5.3*). Fexofenadine hydrochloride should not be used during pregnancy unless clearly necessary.

Lactation

There are no data on the content of human milk after administering fexofenadine hydrochloride. However, when terfenadine was administered to nursing mothers fexofenadine was found to cross into human breast milk. Therefore fexofenadine hydrochloride is not recommended for mothers breast feeding their babies.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and reported adverse events it is unlikely that fexofenadine hydrochloride tablets will produce an effect on the ability to drive or use machines. In objective tests, Fexofenadine has been shown to have no significant effects on central nervous system function. This means that patients may drive or perform tasks that require concentration. However, in order to identify sensitive people who have an unusual reaction to drugs, it is advisable to check the individual response before driving or performing complicated tasks.

4.8 Undesirable effects

In controlled clinical trials in adults the most commonly reported adverse events related to treatment were headache (7.3%), drowsiness (2.3%), nausea (1.5%) and dizziness (1.5%). The incidence of these events observed with fexofenadine was similar to that observed with placebo.

Events related to treatment that have been reported with an incidence of less than 1% include: fatigue, insomnia, nervousness and sleep disorders or paroniria, such as nightmares and tachycardia, palpitations and diarrhoea. In rare cases, rash, urticaria, pruritus, and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnoea, flushing and systemic anaphylaxis have also been reported.

4.9 Overdose

Symptoms of dizziness, drowsiness, fatigue and dry mouth have been reported with overdose of fexofenadine hydrochloride. Single doses up to 800 mg, and doses up to 690 mg twice daily for 1 month, or 240 mg once daily for 1 year have been administered to healthy subjects without the development of clinically significant adverse events. The maximum tolerated dose of fexofenadine hydrochloride has not been established.

Standard measures should be considered to remove any unabsorbed fexofenadine. Symptomatic and supportive treatment is recommended. Haemodialysis does not effectively remove fexofenadine hydrochloride from blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antihistamines for systemic use, ATC code: RO6A X26.

Fexofenadine hydrochloride is a non-sedating H₁antihistamine. Fexofenadine is a pharmacologically active metabolite of terfenadine.

Human histamine wheal and flare studies following single and twice daily doses of fexofenadine hydrochloride demonstrate that the drug exhibits an antihistaminic effect beginning within one hour, achieving maximum at 6 hours and lasting 24 hours. There is no evidence of tolerance to these effects after 28 days of dosing. A positive dose-response relationship between doses of 10mg to 130mg taken orally was found to exist. In this model of antihistaminic activity, it was found that doses of at least 130mg were required to achieve a consistent effect that was maintained over a 24 hour period. Maximum inhibition in skin wheal and flare areas was greater than 80%.

No significant differences in QT_c intervals were observed in adult and adolescent patients with seasonal allergic rhinitis, when given fexofenadine hydrochloride up to 240 mg twice daily for 2 weeks when compared to placebo. Also, no significant change in QT_c intervals was observed in healthy adult subjects given fexofenadine hydrochloride up to 60 mg twice daily for 6 months, 400 mg twice daily for 6.5 days and 240 mg once daily for 1 year, when compared to placebo.

Fexofenadine at concentrations 32 times greater than the therapeutic concentration in man had no effect on the delayed rectifier K⁺ channel cloned from human heart.

Fexofenadine hydrochloride (5-10mg/kg per orally) inhibited antigen induced bronchospasm in sensitised guinea pigs and inhibited histamine release at supratherapeutic concentrations (10- 100µM) from peritoneal mast cells.

5.2 Pharmacokinetic properties

Fexofenadine hydrochloride is rapidly absorbed into the body following oral administration, with T_{max} occurring at approximately 1-3 hours post dose. The mean C_{max} value was approximately 494 ng/ml following the administration of a 180 mg dose once daily.

Fexofenadine is 60-70% plasma protein bound. Fexofenadine undergoes negligible metabolism (hepatic or non-hepatic), as it was the only major compound identified in urine and faeces of animals and man. The plasma concentration profiles of fexofenadine follow a bi-exponential decline with a terminal elimination half-life ranging from 11 to 15 hours after multiple dosing. The single and multiple dose pharmacokinetics of fexofenadine are linear for oral doses up to 120mg BID. A dose of 240mg BID produced slightly greater than proportional increase (8.8%) in steady state area under the curve, indicating that fexofenadine pharmacokinetics are practically linear at these doses between 40 mg and 240mg taken daily. The major route of elimination is believed to be via biliary excretion while up to 10% of ingested dose is excreted unchanged through the urine.

5.3 Preclinical safety data

Dogs tolerated 450mg/kg administered twice daily for 6 months and showed no toxicity other than occasional emesis. Also, in single dose dog and rodent studies, no treatment-related gross findings were observed following necropsy.

Radiolabelled fexofenadine hydrochloride in tissue distribution studies of the rat indicated that fexofenadine did not cross the blood brain barrier.

Fexofenadine hydrochloride was found to be non-mutagenic in various *in vitro* and *in vivo* mutagenicity tests.

The carcinogenic potential of fexofenadine hydrochloride was assessed using terfenadine studies with supporting pharmacokinetic studies showing fexofenadine hydrochloride exposure (via plasma AUC values). No evidence of carcinogenicity was observed in rats and mice given terfenadine (up to 150mg/kg/day).

In a reproductive toxicity study in mice, fexofenadine hydrochloride did not impair fertility, was not teratogenic and did not impair pre- or postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline Cellulose
Maize Starch
Magnesium Stearate
Croscarmellose Sodium
Povidone

Film-coating:
Hypromellose (E464)
Macrogol (PEG 400)
Macrogol (PEG 4000)
Titanium Dioxide (E171)
Iron Oxide Yellow (E172)
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store the tablets in the original package. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Alu blister packs of 7, 10, 15, 20, 30, 50, 100 or 500 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

STD Chemicals Ltd,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 36390 / 0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2011

10 DATE OF REVISION OF THE TEXT

19/09/2011

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET Fexofenadine Hydrochloride 120 mg & 180 mg Film-coated Tablets (Fexofenadine Hydrochloride)

The name of this medicine is Fexofenadine Hydrochloride 120 mg & 180 mg Film-Coated Tablets which will be referred to as Fexofenadine Tablets throughout this leaflet.

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 your 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 the leaflet, please tell your doctor or pharmacist.

In this leaflet

1. What Fexofenadine Tablets are and what they are used for
2. Before you take Fexofenadine Tablets
3. How to take Fexofenadine Tablets
4. Possible side effects
5. How to store Fexofenadine Tablets
6. Further Information

1. WHAT FEXOFENADINE TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient in your tablets is fexofenadine hydrochloride, which belongs to a group of medicines called antihistamines. It can be used to relieve the symptoms of:

- 120 mg : hay fever (seasonal allergic rhinitis), such as sneezing, itchy and runny nose and red, itchy and watery eyes
- 180 mg : long term allergic skin reactions (chronic idiopathic urticaria) such as itching, swelling and rashes
- Fexofenadine Tablets are not suitable for children under 12 years of age.

2. BEFORE YOU TAKE FEXOFENADINE TABLETS

Do not take Fexofenadine Tablets if you:

- have ever had an **allergic reaction** to fexofenadine or any of the other ingredients of the tablets (see section 6 for a full list of ingredients), or if you suspect that you are allergic to any of these ingredients.

Take special care with Fexofenadine Tablets

Before you take Fexofenadine Tablets you should tell your doctor if you:

- have problems with your liver or kidneys
- are elderly
- have heart problems, as fexofenadine, like other antihistamines may cause your heart to beat faster (tachycardia) or you feel your heart beating (palpitations).

Taking other medicines

Please tell your doctor if you are taking or have recently taken any of the following medicines, as they may decrease or increase the effect of Fexofenadine Tablets and vice versa.

- Erythromycin (an antibiotic)
- Ketoconazole (a treatment for fungal infections)
- Antacids containing aluminium and magnesium

It is recommended that you leave about 2 hours between the time that you take Fexofenadine Tablets and your antacids.

It may still be alright for you to take Fexofenadine Tablets but only your doctor will be able to decide what is suitable for you.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, think you might be pregnant, are planning to become pregnant or are breast-feeding.

Do not take Fexofenadine Tablets if you are pregnant, unless prescribed. Fexofenadine Tablets are not recommended during breast-feeding.

Driving and using machines

It is unlikely that Fexofenadine Tablets will affect your ability to drive or use machines. However, you should check that these tablets do not make you feel sleepy or dizzy before driving or operating machinery.

3. HOW TO TAKE FEXOFENADINE TABLETS

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

Dosage:

Adults and children aged 12 years and over

The recommended dose is one tablet (120 mg or 180 mg) daily. Take your tablet with water before a meal.

If you take more Fexofenadine Tablets than you should

If you have accidentally taken more than the prescribed dose, contact your nearest hospital casualty department or tell your doctor or pharmacist immediately. Remember to take the pack and any remaining tablets with you.

The most common signs of overdose are dizziness, drowsiness, fatigue and dry mouth.

If you forget to take Fexofenadine Tablets

Simply leave out dose and then take your next dose at the right time. **Do not** take a double dose or make up for a missed dose.

If you stop taking Fexofenadine Tablets

Tell your doctor if you want to stop taking Fexofenadine Tablets before you have finished your course of treatment. If you stop taking Fexofenadine Tablets earlier than planned, your symptoms may return.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fexofenadine Tablets can cause side effects, although not everybody gets them. If you get any of the following symptoms after taking these tablets you should contact your doctor or pharmacist immediately as these may be signs of a serious allergic reaction:

- **Swelling of the face, lips, tongue or throat and difficulty breathing.**

The following side effects have also been reported:

- **Common** (occurring in less than 1 in 10 but more than 1 in 100 patients):
 - headache
 - drowsiness
 - feeling sick (nausea)
 - dizziness
- **Uncommon** (occurring in less than 1 in 100 but more than 1 in 1,000 patients):
 - difficulty sleeping (insomnia)
 - tiredness or sleepiness
 - sleeping disorders
 - bad dreams
 - nervousness
 - fast or irregular heart beat
 - diarrhoea
- **Rare** (occurring in less than 1 in 1,000 but more than 1 in 10,000 patients):
 - skin rash and itching,
 - hives,
 - serious allergic reaction which can cause swelling of the face, lips, tongue or throat
 - difficulty breathing.

If any of these 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 FEXOFENADINE TABLETS

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date (Exp.) stated on both blister and carton. The expiry date refers to the last day of the month. Store your tablets in the original package.

This medicinal product does not require any special temperature storage condition.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fexofenadine Tablets contain:

The active ingredient is fexofenadine hydrochloride. Each Film-Coated tablet contains 120 mg or 180mg of fexofenadine hydrochloride.

The other ingredients are:-

Tablet core:

Microcrystalline Cellulose, Maize Starch, Magnesium Stearate, Croscarmellose Sodium, Povidone.

Film coating:

Hypromellose (E464), Macrogol (PEG 400), Macrogol (PEG 4000), Titanium Dioxide (E171), Iron Oxide Yellow (E172). The film-coating on the 120 mg tablet also contains Iron Oxide Red (E172).

What Fexofenadine Tablets looks like and the contents of the pack:

Fexofenadine 120 mg Film-coated Tablets are peach coloured, oblong, biconvex, film coated tablets.

Fexofenadine 180 mg Film-coated Tablets are yellow coloured, oblong, biconvex, film coated tablets, plain on one side and with a central breakline on the reverse side. The breakline allows division of the tablet.

Your medicine is available in PVC/PVDC/Alu blister packs of 30 tablets.

Marketing Authorisation Holder and Manufacturer:

The Product Licence holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The manufacturer responsible for batch release is Neolab Ltd, 57 High Street, Odiham, Hants, RG29 1LF.

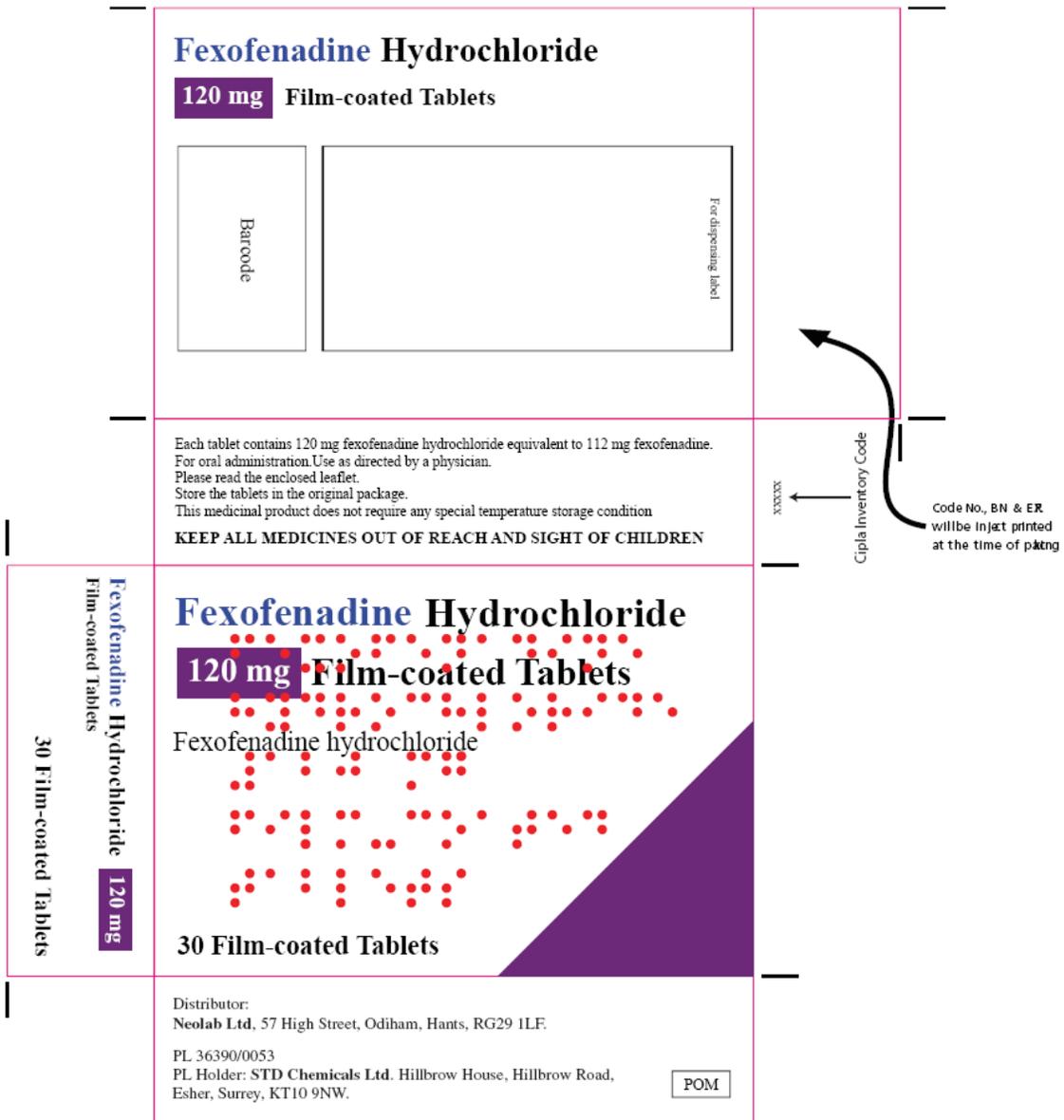
This information is available in alternative formats upon request.

This leaflet was last revised in August 2011.

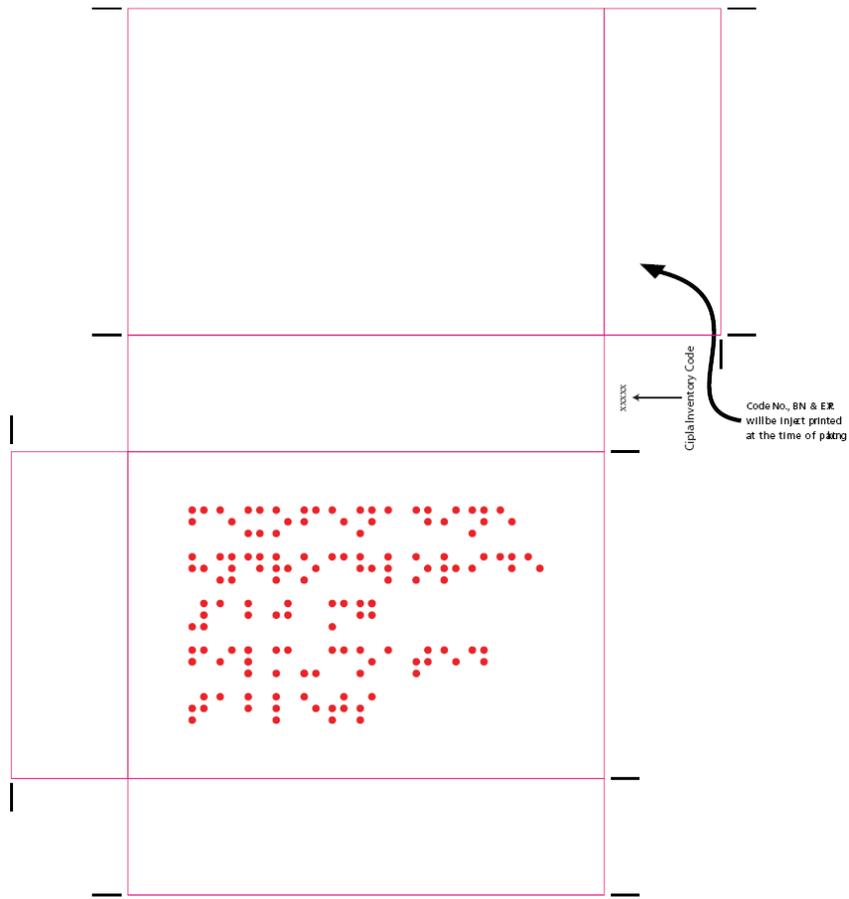
LABELLING

Fexofenadine Hydrochloride 120 mg Film-coated Tablets

Carton for blisters



Carton showing Braille



Braille

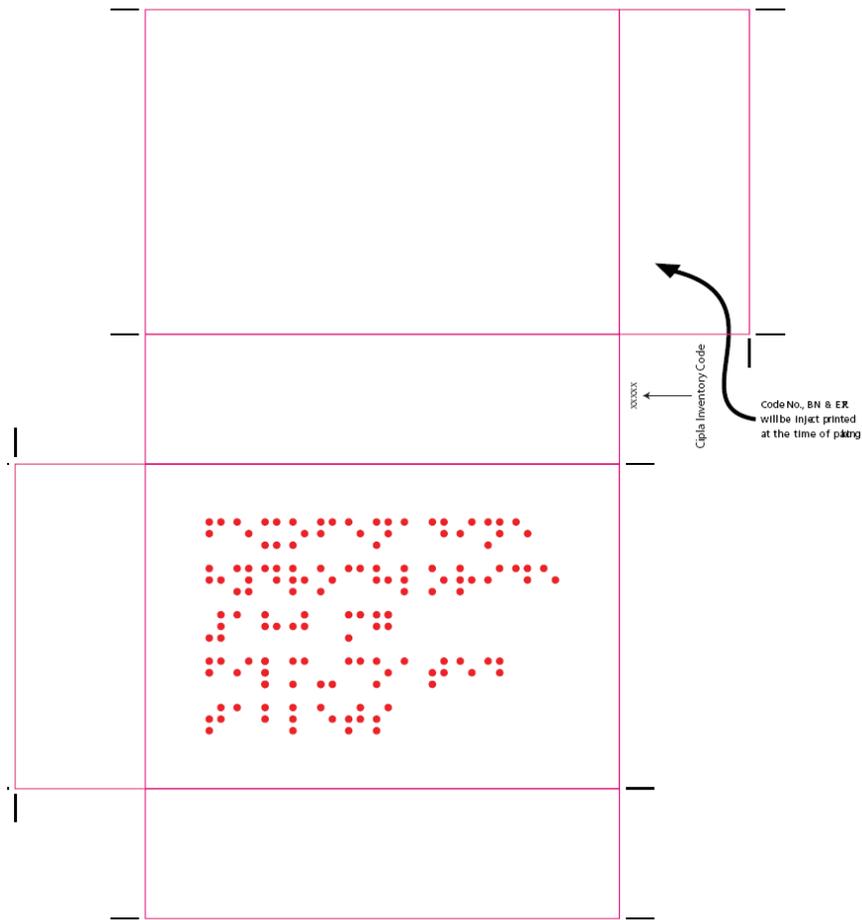
F E X O F E N A D I N E
H Y D R O C H L O R I D E
1 2 0 mg
F I L M - C O A T E D
T A B L E T S

Fexofenadine Hydrochloride 180 mg Film-coated Tablets

Carton for blisters

<p>Fexofenadine Hydrochloride 180 mg Film-coated Tablets</p> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; padding: 5px; text-align: center;">Barcode</div> <div style="border: 1px solid black; padding: 5px; text-align: center;">For dispensing label</div> </div>	
<p>Each tablet contains 180 mg fexofenadine hydrochloride equivalent to 168 mg fexofenadine. For oral administration. Use as directed by a physician. Please read the enclosed leaflet. Store the tablets in the original package. This medicinal product does not require any special temperature storage condition</p> <p>KEEP ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN</p>	<p>XXXXXX Cipla Inventory Code Code No., BN & ER will be in-jact printed at the time of p&trng</p>
<p>Fexofenadine Hydrochloride Film-coated Tablets 30 Film-coated Tablets</p>	<p>Fexofenadine Hydrochloride 180 mg Film-coated Tablets</p> <p>Fexofenadine hydrochloride</p> <p>30 Film-coated Tablets</p>
	<p>Distributor: Neolab Ltd, 57 High Street, Odiham, Hants, RG29 1LF. PL 36390/0054 MA Holder: STD Chemicals Ltd. Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.</p> <div style="border: 1px solid black; padding: 2px; display: inline-block;">POM</div>

Carton showing Braille



Braille

F E X O F E N A D I N E
H Y D R O C H L O R I D E
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T A B L E T S