CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207947Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use UPTRAVI® safely and effectively. See full prescribing information for UPTRAVI®.

UPTRAVI® (selexipag) tablets, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

UPTRAVI® is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. (1.1)

DOSAGE AND ADMINISTRATION

- Starting dose: 200 mcg twice daily. (2.1)
- Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily. (2.1)
- Maintenance dose is determined by tolerability. (2.1)
- Moderate hepatic impairment: Starting dose 200 mcg once daily, increase the dose by 200 mcg once daily at weekly intervals to the highest tolerated dose up to 1600 mcg. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment. (5.1)

ADVERSE REACTIONS

Adverse reactions occurring more frequently (>5%) on UPTRAVI compared to placebo are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP2C8 inhibitors: increased exposure to selexipag and its active metabolite. Avoid concomitant use. (7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: discontinue UPTRAVI or breastfeeding. (8.2)
- Severe hepatic impairment: Avoid use. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

UPTRAVI is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%) *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dose of UPTRAVI is 200 micrograms (mcg) given twice daily. Tolerability may be improved when taken with food *[see Clinical Pharmacology (12.3)]*.

Increase the dose in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.

Do not split, crush, or chew tablets.

2.2 Interruptions and Discontinuations

If a dose of medication is missed, patients should take a missed dose as soon as possible unless the next dose is within the next 6 hours.

If treatment is missed for 3 days or more, restart UPTRAVI at a lower dose and then retitrate.

2.3 Dosage Adjustment in Patients with Hepatic Impairment

No dose adjustment of UPTRAVI is necessary for patients with mild hepatic impairment (Child-Pugh class A).

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of UPTRAVI is 200 mcg once daily. Increase in increments of 200 mcg once daily at weekly intervals, as tolerated *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

3 DOSAGE FORMS AND STRENGTHS

UPTRAVI is available in the following strengths:

- 200 mcg [Light yellow tablet debossed with 2]
- 400 mcg [Red tablet debossed with 4]
- 600 mcg [Light violet tablet debossed with 6]
- 800 mcg [Green tablet debossed with 8]
- 1000 mcg [Orange tablet debossed with 10]
- 1200 mcg [Dark violet tablet debossed with 12]
- 1400 mcg [Dark yellow tablet debossed with 14]
- 1600 mcg [Brown tablet debossed with 16]

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of UPTRAVI has been evaluated in a long-term, placebo-controlled study enrolling 1156 patients with symptomatic PAH (GRIPHON study) *[see Clinical Studies (14)]*. The exposure to UPTRAVI in this trial was up to 4.2 years with median duration of exposure of 1.4 years.

Table 1 presents adverse reactions more frequent on UPTRAVI than on placebo by >3%.

Table 1 Adverse Reactions

	UPTRAVI	**Placebo**
Adverse Reaction	**N=575**	**N=577**
Headache	65%	32%
Diarrhea	42%	18%
Jaw pain	26%	6%
Nausea	33%	18%
Myalgia	16%	6%
Vomiting	18%	9%
Pain in Extremity	17%	8%
Flushing	12%	5%
Arthralgia	11%	8%
Anemia	8%	5%
Decreased appetite	6%	3%
Rash	11%	8%

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

Laboratory Test Abnormalities

Hemoglobin

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from −0.34 to −0.02 g/dL in the selexipag group compared to −0.05 to 0.25 g/dL in the placebo group. A decrease in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

7 DRUG INTERACTIONS

7.1 Strong CYP2C8 Inhibitors

Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite. Avoid concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with UPTRAVI in pregnant women. Animal reproduction studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival. A slight reduction in maternal as well as in fetal body weight was observed when pregnant rats were administered selexipag during organogenesis at a dose producing an exposure approximately 47 times that in humans at the maximum recommended human dose. No adverse developmental outcomes were observed with oral administration of selexipag to pregnant rabbits during organogenesis at exposures up to 50 times the human exposure at the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day (up to 47 times the exposure at the maximum recommended human dose of 1600 mcg twice daily on an area under the curve [AUC] basis) during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg (up to 50 times the exposure to the active metabolite at the maximum recommended human dose of 1600 mcg twice daily on an AUC basis) during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

8.2 Lactation

It is not known if UPTRAVI is present in human milk. Selexipag or its metabolites were present in the milk of rats. Because many drugs are present in the human milk and because of the

potential for serious adverse reactions in nursing infants, discontinue nursing or discontinue UPTRAVI.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1368 subjects in clinical studies of UPTRAVI 248 subjects were 65 years of age and older, while 19 were 75 and older. No overall differences were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity cannot be ruled out.

8.6 Patients with Hepatic Impairment

No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C). Avoid use of UPTRAVI in patients with severe hepatic impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No adjustment to the dosing regimen is needed in patients with estimated glomerular filtration rate > 15 mL/min/1.73 m^2.

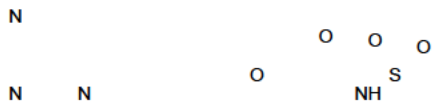
There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with glomerular filtration rates < 15 mL/min/1.73 m^2 *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Isolated cases of overdose up to 3200 mcg were reported. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein-bound.

11 DESCRIPTION

UPTRAVI (selexipag) is a selective non-prostanoid IP prostacyclin receptor agonist. The chemical name of selexipag is 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-*N*-(methylsulfonyl) acetamide. It has a molecular formula of $C_{26}H_{32}N_4O_4S$ and a molecular weight of 496.62. Selexipag has the following structural formula:



Selexipag is a pale yellow crystalline powder that is practically insoluble in water. In the solid state selexipag is very stable, is not hygroscopic, and is not light sensitive.

Depending on the dose strength, each round film-coated tablet for oral administration contains 200, 400, 600, 800, 1000, 1200, 1400, or 1600 mcg of selexipag. The tablets include the following inactive ingredients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, and magnesium stearate. The tablets are film coated with a coating material containing hypromellose, propylene glycol, titanium dioxide, carnauba wax along with mixtures of iron oxide red, iron oxide yellow or iron oxide black.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selexipag is an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. Selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP_{1-4}, DP, FP and TP).

12.2 Pharmacodynamics

Cardiac electrophysiology:

At the maximum tolerated dose of 1600 mcg twice daily, selexipag does not prolong the QT interval to any clinically relevant extent.

Platelet aggregation:

Both selexipag and its active metabolite caused concentration-dependent inhibition of platelet aggregation *in vitro* with an IC_{50} of 5.5 μM and 0.21 μM, respectively. However, at clinically relevant concentrations, there was no effect on platelet aggregation test parameters as seen following multiple-dose administrations of selexipag in healthy subjects from 400 mcg up to 1800 mcg twice daily.

Pulmonary hemodynamics:

A Phase 2 clinical study assessed hemodynamic variables after 17 weeks of treatment in patients with PAH WHO Functional Class II–III and concomitantly receiving endothelin receptor antagonists (ERAs) and/or phosphodiesterase type 5 (PDE-5) inhibitors. Patients titrating selexipag to an individually tolerated dose (200 mcg twice daily increments up to 800 mcg twice daily) (N=33) achieved a statistically-significant mean reduction in pulmonary vascular resistance of 30.3% (95% confidence interval [CI] −44.7%, −12.2%) and an increase in cardiac

index (median treatment effect) of 0.41 L/min/m^2 (95% CI 0.10, 0.71) compared to placebo (N=10).

Drug interaction:

In a study in healthy subjects, selexipag (400 mcg twice a day) did not influence the pharmacodynamic effect of warfarin on the international normalized ratio.

12.3 Pharmacokinetics

The pharmacokinetics of selexipag and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of selexipag and the active metabolite, after both single- and multiple-dose administration, were dose-proportional up to a single dose of 800 mcg and multiple doses of up to 1800 mcg twice daily. No accumulation in plasma, either of parent compound or active metabolite, occurred after multiple-dose administration.

In healthy subjects, inter-subject variability in exposure (area under the curve over a dosing interval, AUC) at steady-state was 43% and 39% for selexipag and the active metabolite, respectively. Intra-subject variability in exposure was 24% and 19% for selexipag and the active metabolite, respectively.

Exposures to selexipag and the active metabolite at steady-state in PAH patients and healthy subjects were similar. The pharmacokinetics of selexipag and the active metabolite in PAH patients were not influenced by the severity of the disease and did not change with time.

Both in healthy subjects and PAH patients, exposure at steady-state to the active metabolite is approximately 3- to 4-fold that of selexipag.

Absorption

Upon oral administration, maximum observed plasma concentrations of selexipag and its active metabolite after oral administration are reached within about 1–3 hours and 3–4 hours, respectively.

In the presence of food, the absorption of selexipag was prolonged resulting in a delayed time to peak concentration (T_{max}) and ~30% lower peak plasma concentration (C_{max}). The exposure to selexipag and the active metabolite (AUC) did not significantly change in the presence of food.

Distribution

Selexipag and its active metabolite are highly bound to plasma proteins (approximately 99% in total and to the same extent to albumin and alpha1-acid glycoprotein).

Metabolism

Selexipag undergoes enzymatic hydrolysis of the acylsulfonamide by hepatic carboxylesterase 1, to yield the active metabolite. Oxidative metabolism catalyzed by CYP3A4 and CYP2C8 leads to the formation of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceeds 3% of the total drug-related material.

Elimination

Elimination of selexipag is predominately via metabolism with a mean terminal half-life of 0.8-2.5 hours. The active metabolite has a terminal half-life of 6.2-13.5 hours. The apparent oral clearance of selexipag is on average 35 L/hour.

Excretion

In a study in healthy subjects with radiolabeled selexipag, approximately 93% of radioactive drug material was eliminated in feces and only 12% in urine. Neither selexipag nor its active metabolite were found in urine.

Specific Populations:

No clinically relevant effects of sex, race, age or body weight on the pharmacokinetics of selexipag and its active metabolite have been observed in healthy subjects or PAH patients.

Age:

The pharmacokinetic variables (C_{max} and AUC) were similar in adult and elderly subjects up to 75 years of age. There was no effect of age on the pharmacokinetics of selexipag and the active metabolite in PAH patients.

Hepatic Impairment:

In subjects with mild *(Child-Pugh class A)* or moderate *(Child-Pugh class B)* hepatic impairment, exposure to selexipag was 2- and 4-fold that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. *[see Use in Specific Populations (8.6)]*.

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, the exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in these patients during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice-daily regimen.

Renal Impairment:

A 40-70% increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate > 15 mL/min/1.73 m^2 and < 30 mL/min/1.73 m^2) *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies:

In vitro studies

Selexipag is hydrolyzed to its active metabolite by hepatic carboxylesterase 1. Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8 and CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp,

and the active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP).

Selexipag and its active metabolite do not inhibit or induce hepatic cytochrome P450 enzymes at clinically relevant concentrations. Selexipag and its active metabolite do not inhibit hepatic or renal transport proteins.

The effect of strong inhibitors of CYP2C8 (such as gemfibrozil) on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite *[see Drug Interactions (7.1)]*.

The results on in vivo drug interaction studies are presented in Figure 1.

Figure 1 Effect of Other Drugs on UPTRAVI and its Active Metabolite (A) and Effect of UPTRAVI on Warfarin (B)

*ERA and PDE-5 inhibitor data from GRIPHON.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In the 2-year carcinogenicity studies, chronic oral administration of selexipag revealed no evidence of carcinogenic potential in rats at 100 mg/kg/day and mice at 500 mg/kg/day. The exposures were more than 25-fold human exposure.

Mutagenesis: Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.

Fertility: The no effect dose for effects on fertility was 60 mg/kg/day in a study in which rats were administered selexipag orally. This dose corresponded to an exposure of 175-times (active metabolite) the human therapeutic exposure.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension

The effect of selexipag on progression of PAH was demonstrated in a multi-center, double-blind, placebo-controlled, parallel group, event-driven study (GRIPHON) in 1156 patients with symptomatic (WHO Functional Class I [0.8%], II [46%], III [53%], and IV [1%]) PAH. Patients were randomized to either placebo (N = 582), or UPTRAVI (N = 574). The dose was increased in weekly intervals by increments of 200 mcg twice a day to the highest tolerated dose up to 1600 mcg twice a day.

The primary study endpoint was the time to first occurrence up to end-of-treatment of: a) death, b) hospitalization for PAH, c) PAH worsening resulting in need for lung transplantation, or balloon atrial septostomy, d) initiation of parenteral prostanoid therapy or chronic oxygen therapy, or e) other disease progression based on a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy.

The mean age was 48 years, the majority of patients were white (65%) and female (80%). Nearly all patients were in WHO Functional Class II and III at baseline.

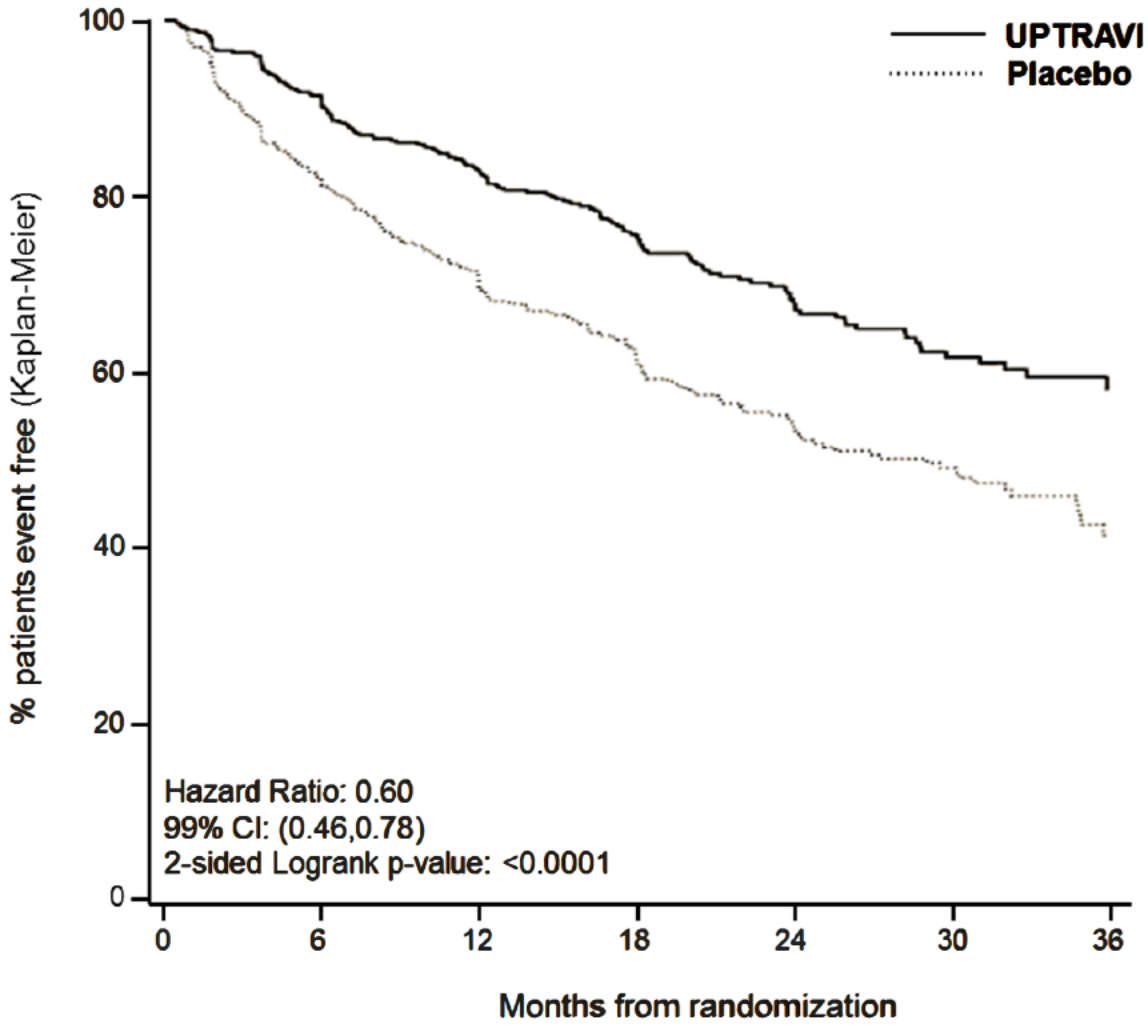
Idiopathic or heritable PAH was the most common etiology in the study population (58%) followed by PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%), drugs and toxins (2%), and HIV (1%).

At baseline, the majority of enrolled patients (80%) were being treated with a stable dose of an endothelin receptor antagonist (15%), a PDE-5 inhibitor (32%), or both (33%).

Patients on selexipag achieved doses within the following groups: 200 - 400 mcg (23%), 600 - 1000 mcg (31%) and 1200 - 1600 mcg (43%).

Treatment with UPTRAVI resulted in a 40% reduction (99% CI: 22 to 54%; two-sided log-rank p-value < 0.0001) of the occurrence of primary endpoint events compared to placebo (Table 2; Figure 2). The beneficial effect of UPTRAVI was primarily attributable to a reduction in hospitalization for PAH and a reduction in other disease progression events (Table 2). The observed benefit of UPTRAVI was similar regardless of the dose achieved when patients are titrated to their highest tolerated dose *[see Dosage and Administration (2.1)]*.

Figure 2 **Kaplan-Meier Estimates of the First Morbidity-Mortality Event in GRIPHON**



UPTRAVI patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

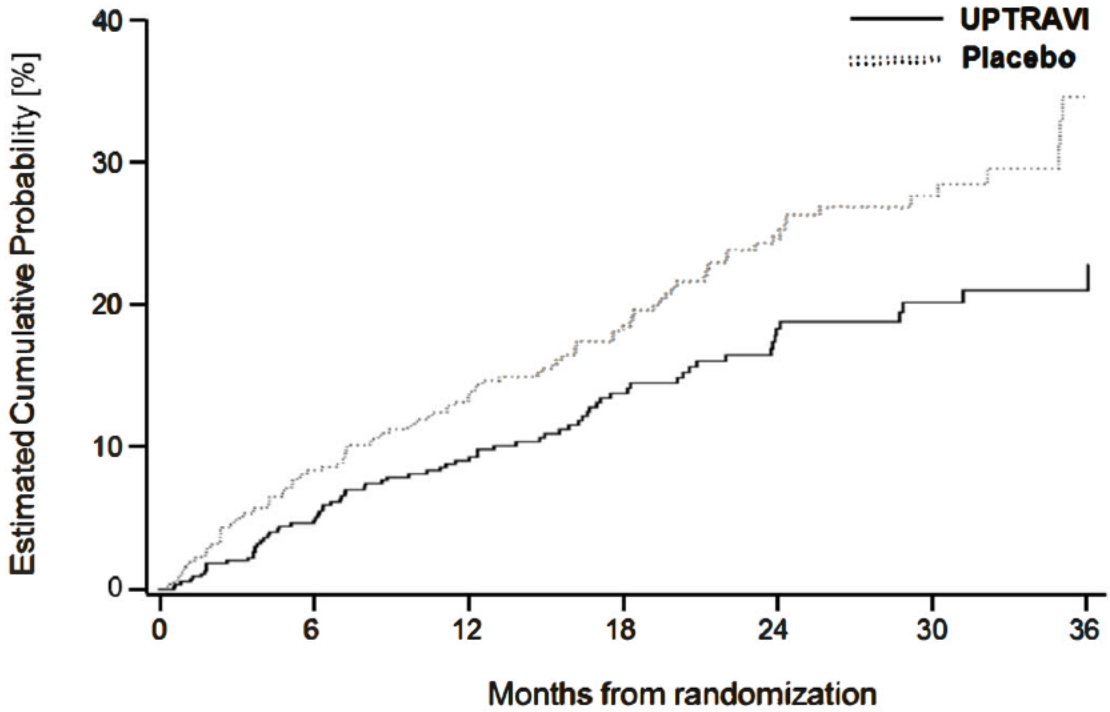
Table 2 Primary Endpoints and Related Components in GRIPHON

	UPTRAVI N=574		Placebo N=582		Hazard Ratio (99% CI)	p-value
	n	%	n	%		
Primary endpoint events up to the end of treatment						
All primary endpoint events	155	27.0	242	41.6	0.60 [0.46,0.78]	<0.0001
As first event:						
• Hospitalization for PAH	78	13.6	109	18.7		
• Other disease Progression (Decrease in 6MWD plus worsening functional class or need for other therapy)	38	6.6	100	17.2		
• Death	28	4.9	18	3.1		
• Parenteral prostanoid or chronic oxygen therapy	10	1.7	13	2.2		
• PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	1	0.2	2	0.3		

It is not known if the excess number of deaths in the selexipag group is drug-related because there were so few deaths and the imbalance was not observed until 18 months into GRIPHON.

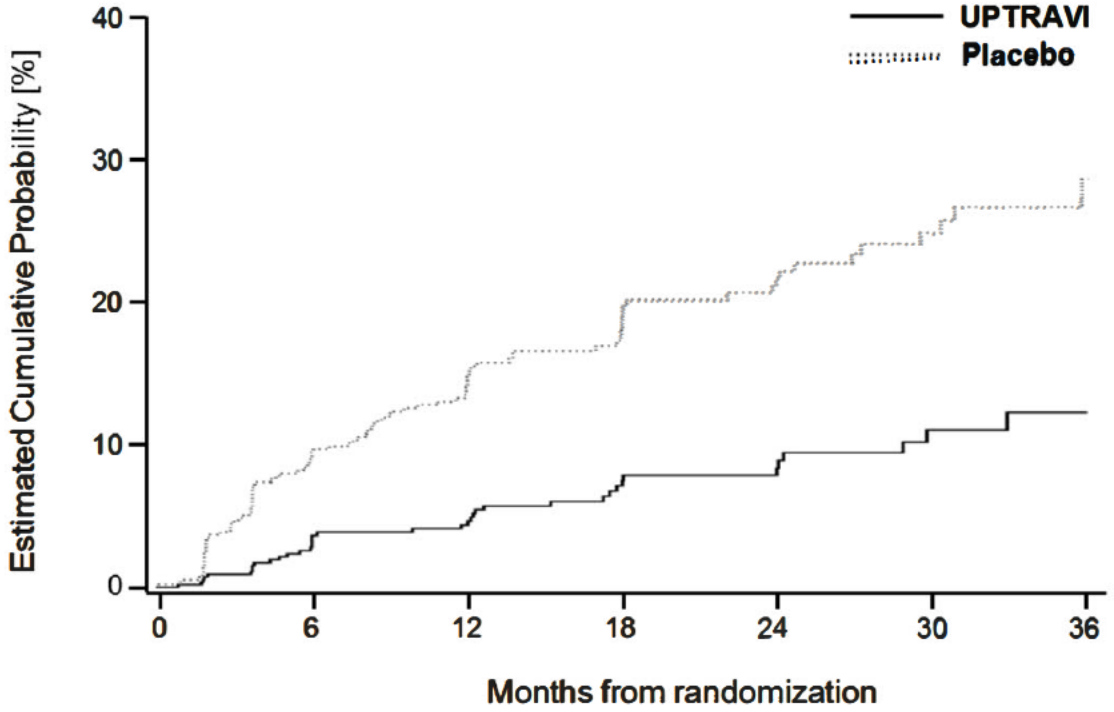
Figures 3A, B and C show time to first event analyses for primary endpoint components of hospitalization for PAH (A), other disease progression (B), and death (C)—all censored 7 days after any primary end point event (because many patients on placebo transitioned to open-label UPTRAVI at this point).

Figure 3 A Hospitalization for PAH as the First Endpoint in GRIPHON



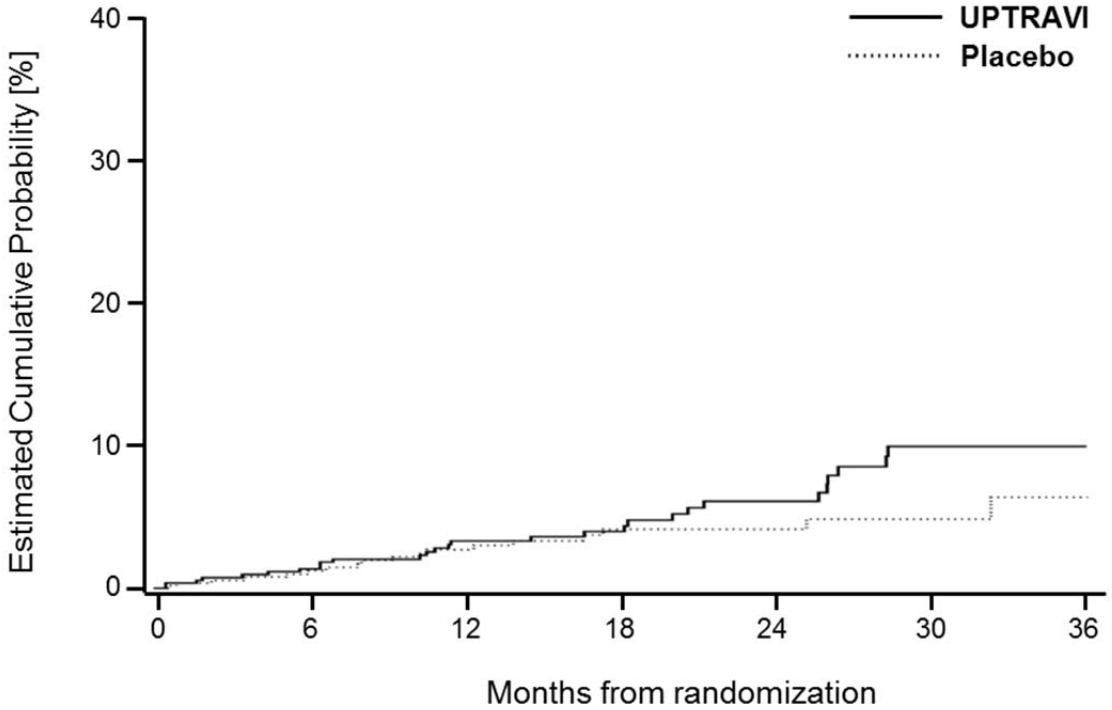
UPTRAVI patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

Figure 3B Disease Progression as the First Endpoint in GRIPHON



UPTRAVI patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

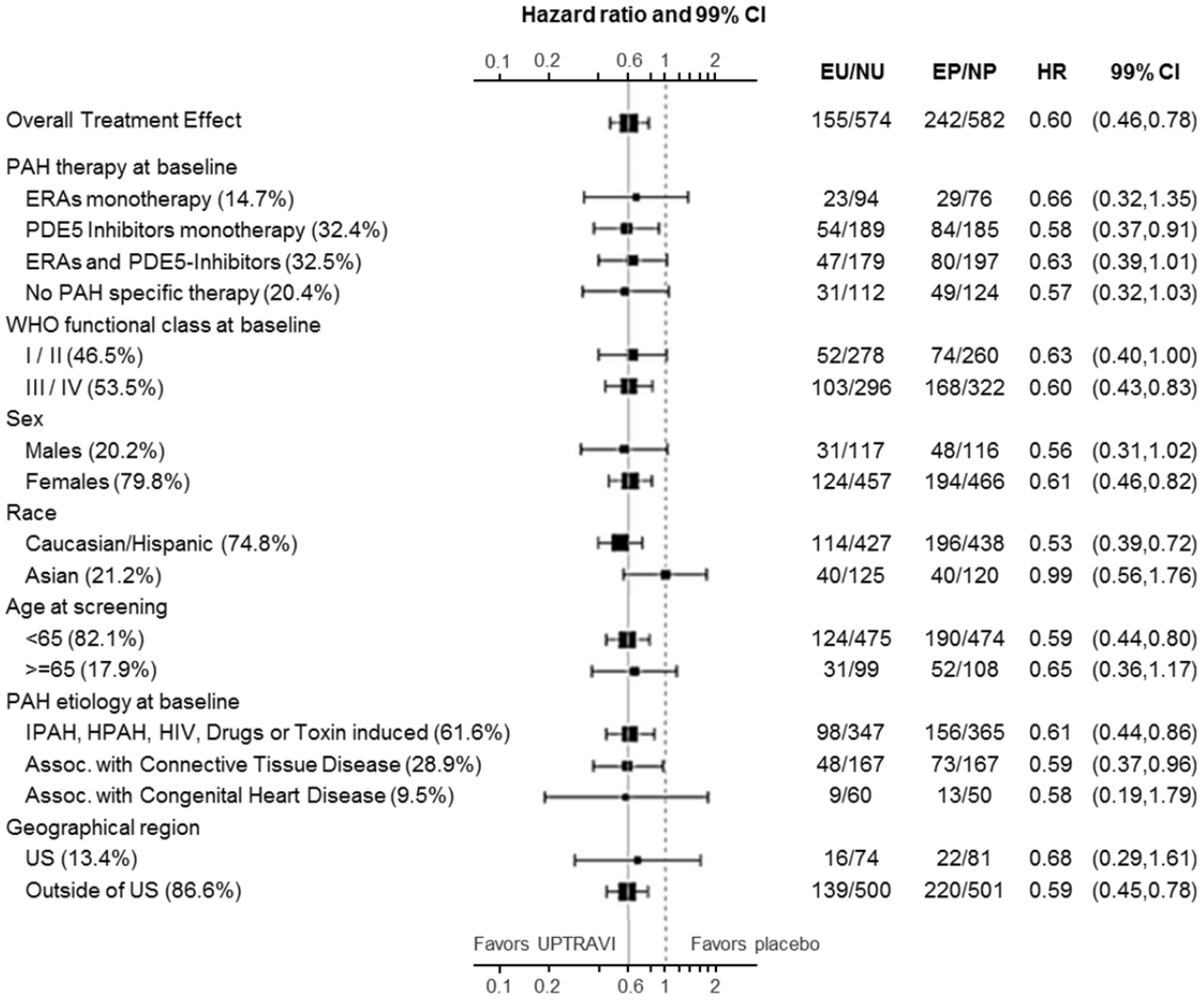
Figure 3 C Death as the First Endpoint in GRIPHON



UPTRAVI patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

The treatment effect of UPTRAVI on time to first primary event was consistent irrespective of background PAH therapy (i.e., in combination with ERA, PDE5i, or both, or without background therapy) (Figure 4).

Figure 4 Subgroup Analyses of the Primary Endpoint in GRIPHON



Note: Race group "Other" is not displayed in analysis, as the population is less than 30. EU = Number of UPTRAVI patients with events, NU = Number of patients randomized to UPTRAVI, EP = Number of Placebo patients with events, NP = Number of patients randomized to Placebo, HR = Hazard Ratio, CI = Confidence Interval, the size of the squares represent the number of patients in the subgroup.

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all were pre-specified. The 99% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

6-Minute Walk Distance (6MWD)

Exercise capacity was evaluated as a secondary endpoint. Median absolute change from baseline to week 26 in 6MWD measured at trough (i.e. at approximately 12 hours post-dose) was +4 meters with UPTRAVI and -9 meters in the placebo group. This resulted in a placebo-corrected median treatment effect of 12 meters (99% CI: 1, 24 meters;two-sided p = 0.005).

16 HOW SUPPLIED/STORAGE AND HANDLING

UPTRAVI (selexipag) film-coated, round tablets are supplied in the following configurations:

Strength (mcg)	**Color**	**Debossing**	**NDC-XXX Bottle of 60**	**NDC-XXX Bottle of 140**
200	Light yellow	2	66215-602-06	66215-602-14
400	Red	4	66215-604-06	Not Applicable
600	Light violet	6	66215-606-06	Not Applicable
800	Green	8	66215-608-06	Not Applicable
1000	Orange	10	66215-610-06	Not Applicable
1200	Dark violet	12	66215-612-06	Not Applicable
1400	Dark yellow	14	66215-614-06	Not Applicable
1600	Brown	16	66215-616-06	Not Applicable

Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Package Insert).

Inform patients:

- what to do if they miss a dose
- not to split, crush, or chew tablets.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20151221

Patient Information
UPTRAVI (up-TRA-vee)
(selexipag) tablets

Read this Patient Information before you start taking UPTRAVI and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is UPTRAVI?

- UPTRAVI is a prescription medicine used to treat pulmonary arterial hypertension (PAH) which is high blood pressure in the arteries of your lungs.
- UPTRAVI can help slow down the progression of your disease and lower your risk of being hospitalized for PAH.

It is not known if UPTRAVI is safe and effective in children.

What should I tell my healthcare provider before taking UPTRAVI?

Before you take UPTRAVI, tell your healthcare provider if you:

- have liver problems
- have narrowing of the pulmonary veins, a condition called pulmonary veno-occlusive disease
- are pregnant or plan to become pregnant. It is not known if UPTRAVI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if UPTRAVI passes into your breast milk. You and your healthcare provider should decide if you will take UPTRAVI or breastfeed. You should not do both.
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. UPTRAVI and other medicines may affect each other causing side effects. Do not start any new medicine until you check with your healthcare provider.

How should I take UPTRAVI?

- Take UPTRAVI exactly as your healthcare provider tells you to take it. Do not stop taking UPTRAVI unless your healthcare provider tells you to stop.
- Your healthcare provider will slowly increase your dose to find the dose of UPTRAVI that is right for you.
- If you have side effects, your healthcare provider may tell you to change your dose of UPTRAVI.
- UPTRAVI can be taken with or without food. Taking UPTRAVI with food may help you tolerate UPTRAVI better.
- UPTRAVI is usually taken 2 times each day.
- Swallow UPTRAVI tablets whole. Do not split, crush or chew UPTRAVI tablets.
- If you miss a dose of UPTRAVI, take it as soon as you remember. If your next scheduled dose is due within 6 hours, skip the missed dose. Take the next dose at your regular time.
- If you miss 3 or more days of UPTRAVI, call your healthcare provider to see if your dose needs to be changed.
- If you take too much UPTRAVI, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of UPTRAVI?

The most common side effects of UPTRAVI include:

- headache
- jaw pain
- muscle pain
- pain in arms or legs
- pain in joints
- decreased appetite
- diarrhea
- nausea
- vomiting
- flushing
- low red blood cell count
- rash

These are not all of the possible side effects of UPTRAVI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store UPTRAVI?

- Store UPTRAVI tablets at room temperature between 68°F and 77°F (20°C and 25°C).

Keep UPTRAVI and all medicines out of the reach of children.

General information about the safe and effective use of UPTRAVI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use UPTRAVI for a condition for which it was not prescribed. Do not give UPTRAVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about UPTRAVI that is written for health professionals.

What are the ingredients in UPTRAVI?

Active ingredient: selexipag

Inactive ingredients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, and magnesium stearate. The tablets are film coated with a coating material containing hypromellose, propylene glycol, titanium dioxide, carnauba wax along with iron oxide red, iron oxide yellow, or iron oxide black.

Manufactured for: Actelion Pharmaceutical US, Inc. 5000 Shoreline Court, Ste. 200 South San Francisco, CA 94080, USA
ACT20141205

For more information, call 1-866-228-3546 or go to www.UPTRAVI.com.

The Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 12/2015

Each tablet contains 200 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-602-06
60 tablets Rx only

Uptravi
selexipag
tablets
200 mcg

UPT-PIL-200-US-445

Lot.:
Exp.:

N 3 66215 60206 5

(b) (4)

10.11.14 14:43

Product	**Uptravi 200 mcg / 60 tablets**		
Material No.	(b) (4)	**Actelion**	
Replaced No.		Order File	
Country	**US**		
Code No.	**366215602065**	contract manufacturer:	
Dimension	**115 x 30 mm**		
Drawing No.			
		Page **1** of **1**	
Sec. Edge Marks		(b) (4)	

Actelion Pharmaceuticals Ltd		1. Proof	(b) (4)
		2. Proof	
Fontsize	**6 pt**	3. Proof	
technical	**8 pt**	4. Proof	
Used Font	**Gotham / Gotham Cond.**	5. Proof	
		6. Proof	
Colours	(b) (4)		(b) (4)
	(b) (4)		
additional	**Cutting**		

(b) (4)

(b) (4)

Each tablet contains 200 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

(b) (4)

NDC 66215-602-14
140 tablets Rx only

Uptravi®
selexipag
tablets
200 mcg

UPT-PIL-200-US-454

Lot.:
Exp.:

N 3 66215 60214 0

11.11.14 10:02

Product	**Uptravi 200 mcg / 140 tablets**		
Material No.	(b) (4)	**Actelion**	
Replaced No.		Order File	
Country	**US**		
Code No.	**366215602140**	contract manufacturer:	
Dimension	**115 x 30 mm**		
Drawing No.			
		Page 1 of 1	
Sec. Edge Marks		(b) (4)	

Actelion Pharmaceuticals Ltd		1. Proof	(b) (4)
		2. Proof	
Fontsize	**6 pt**	3. Proof	
technical	**8 pt**	4. Proof	
Used Font	**Gotham / Gotham Cond.**	5. Proof	
		6. Proof	
Colours	(b) (4)		(b) (4)
	(b) (4)		
additional	**Cutting**		

(b) (4)

(b) (4)

Each tablet contains 400 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-604-06
60 tablets Rx only

Uptravi®
selexipag
tablets

400 mcg

UPT-PL-400-US-446

Lot.:
Exp.:

N 3 66215 60406 9

UPT-PL-400-US-446 pp01.indd 1 10.11.14 15:14

Product	**Uptravi 400 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-400-US-446**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215604069**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4) (b) (4)		(b) (4)
		Page **1** of **1**			
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Reference ID: 3864143

Each tablet contains 600 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-606-06
60 tablets Rx only

Uptravi®
selexipag
tablets
600 mcg

UPT-PL-600-US-447

Lot.:
Exp.:

N 3 66215 60606 3

UPT-PL-600-US-447 pp01.indd 1 10.11.14 15:29

Product	**Uptravi 600 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-600-US-447**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215606063**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4)		(b) (4)
		Page **1** of **1**	(b) (4)		
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Reference ID: 3864143

Each tablet contains 800 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-608-06
60 tablets Rx only

Uptravi®
selexipag
tablets
800 mcg

UPT-PL-800-US-448

Lot.:
Exp.:

N 3 66215 60806 7

UPT-PL-800-US-448 pp01.indd 1 10.11.14 15:48

Product	**Uptravi 800 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-800-US-448**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215608067**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4)		(b) (4)
		Page **1** of **1**	(b) (4)		
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Reference ID: 3864143

Each tablet contains 1000 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-610-06
60 tablets Rx only

Uptravi®
selexipag
tablets
1000 mcg

UPT-PL-1000-US-449

Lot.:
Exp.:

N 3 66215 61006 0

UPT-PL-1000-US-449 pp01 indd 1 11.11.14 08:47

Product	**Uptravi 1000 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-1000-US-449**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215610060**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4)		(b) (4)
		Page **1** of **1**	(b) (4)		
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Reference ID: 3864143

Each tablet contains 1200 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-612-06
60 tablets Rx only

Uptravi
selexipag
tablets
1200 mcg

UPT-PL-1200-US-450

Lot.:
Exp.:

N 3 66215 61206 4

UPT-PL-1200-US-450 pp01 indd 1 11.11.14 10:06

Product	**Uptravi 1200 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-1200-US-450**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215612064**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4)		(b) (4)
		Page **1** of **1**	(b) (4)		
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Each tablet contains 1400 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-614-06
60 tablets Rx only

Uptravi
selexipag
tablets
1400 mcg

UPT-PL-1400-US-451

Lot.:
Exp.:

N 3 66215 61406 8

UPT-PL-1400-US-451 pp01 indd 1 11.11.14 09:30

Product	**Uptravi 1400 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-1400-US-451**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215614068**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4)		(b) (4)
		Page **1** of **1**	(b) (4)		
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Each tablet contains 1600 mcg of selexipag.
Read the Prescribing Information before use.
Dosage: see package insert.
Store at 20°C to 25°C (68°F to 77°F).
Excursions are permitted between
15°C and 30°C (59°F and 86°F).
[See USP controlled room temperature.]
Keep out of the reach of children.

ACTELION

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

FPO

(b) (4)

NDC 66215-616-06
60 tablets Rx only

Uptravi
selexipag
tablets

1600 mcg

UPT-PL-1600-US-452

Lot.:
Exp.:

N 3 66215 61606 2

UPT-PL-1600-US-452 pp01 indd 1 11.11.14 09:45

Product	**Uptravi 1600 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PL-1600-US-452**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **6 pt**	3. Proof	
Country	**US**		technical **8 pt**	4. Proof	
Code No.	**366215616062**	contract manufacturer:	Used Font **Gotham / Gotham Cond.**	5. Proof	
Dimension	**115 x 30 mm**			6. Proof	
Drawing No.			Colours (b) (4) (b) (4)		(b) (4)
		Page **1** of **1**			
Sec. Edge Marks		(b) (4)	additional **Cutting**		

(b) (4)

(b) (4)

Reference ID: 3864143

(b) (4)

Exp.:

Lot.:

Uptravi selexipag tablets 200 mcg 60 tablets

NDC 66215-602-06

Uptravi selexipag tablets

200 mcg

Rx only
60 tablets

Each tablet contains 200 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-200-US-551
46 x 51 x 85
076 A02

NDC 66215-602-06

Uptravi selexipag tablets

200 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

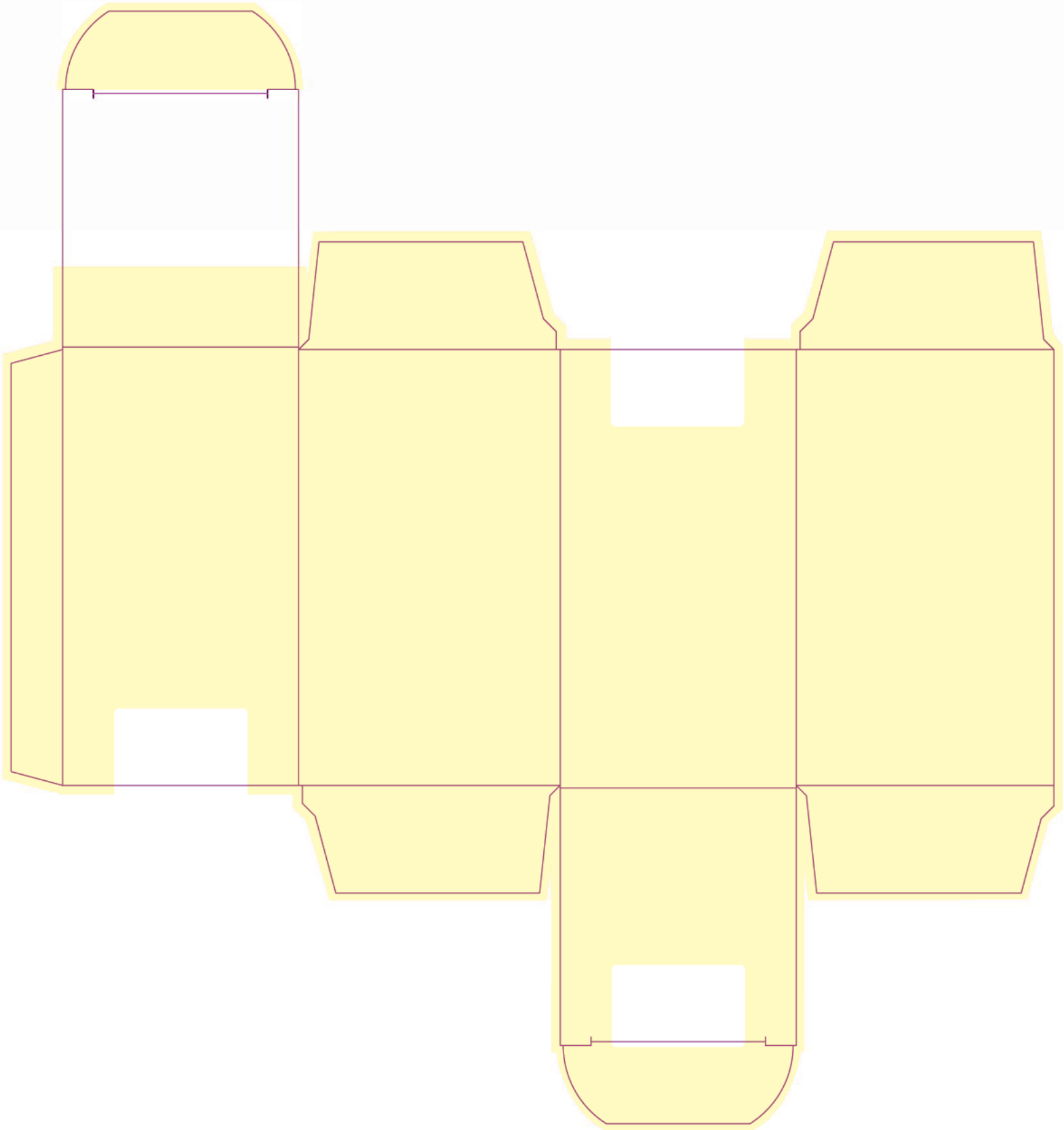
Uptravi selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 200 mcg US, 60 tablets**	
	Mock up code **UPT-PC-200-US-551**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 200 mcg US, 60 tablets**	
	Mock up code **UPT-PC-200-US-551**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

Uptravi selexipag tablets 200 mcg 140 tablets

Lot:

Exp.:

NDC 66215-602-14

Uptravi® selexipag tablets

200 mcg

Rx only
140 tablets

Each tablet contains 200 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-200-US-561
46 x 51 x 85
076 A02

NDC 66215-602-14

Uptravi® selexipag tablets

200 mcg

Rx only
140 tablets

Uptravi® selexipag tablets

Rx only
140 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

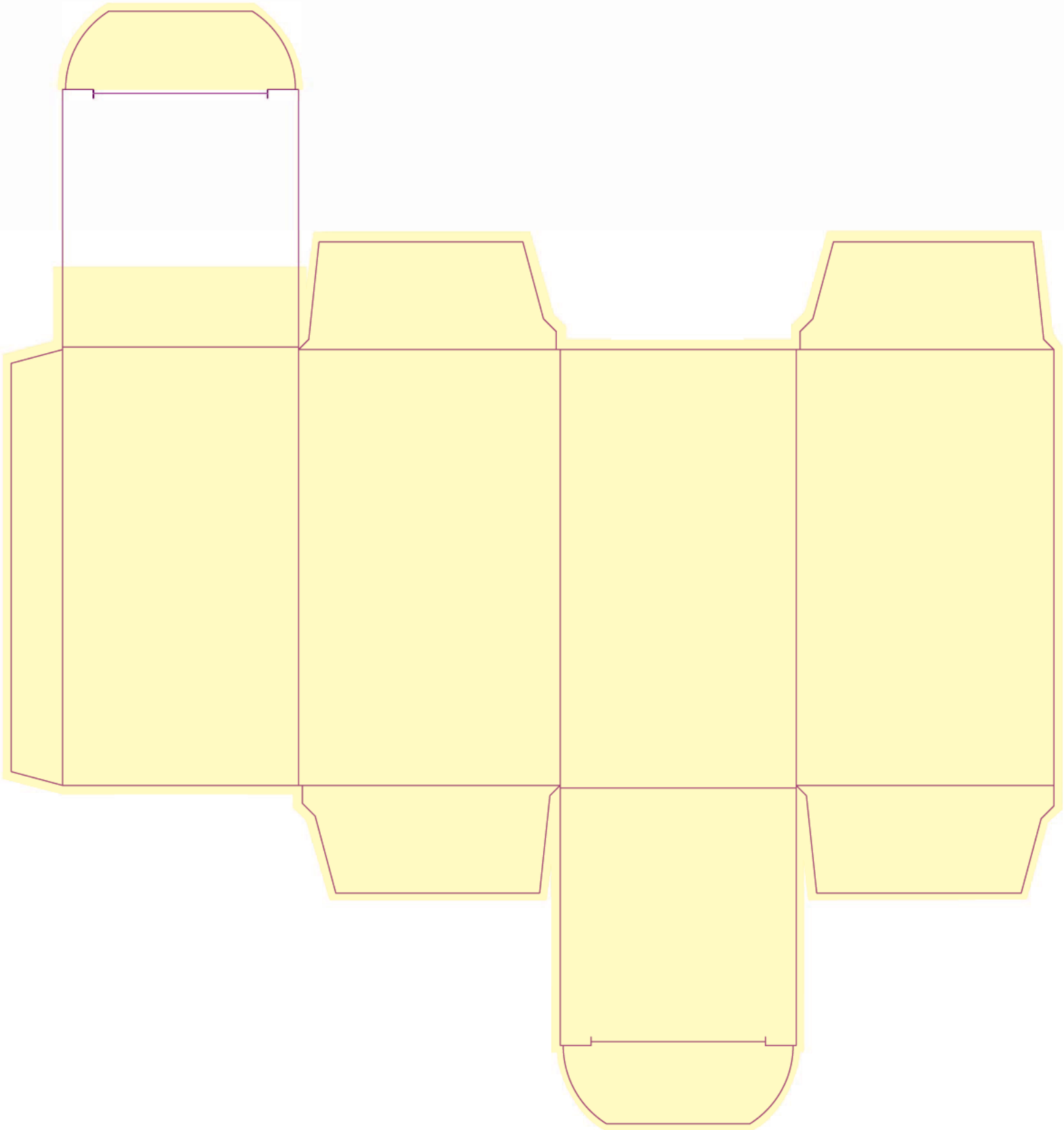
ACTELION

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 200 mcg US, 140 tablets**	
	Mock up code **UPT-PC-200-US-561**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

Reference ID: 3864143



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 200 mcg US, 140 tablets**	
	Mock up code **UPT-PC-200-US-561**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Exp.:

Lot.:

Uptravi selexipag tablets 400 mcg 60 tablets

NDC 66215-604-06

Uptravi® selexipag tablets

400 mcg

Rx only
60 tablets

Each tablet contains 400 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-400-US-554
46 x 51 x 85
076 A02

NDC 66215-604-06

Uptravi® selexipag tablets

400 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

N 3 66215 60406 9

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

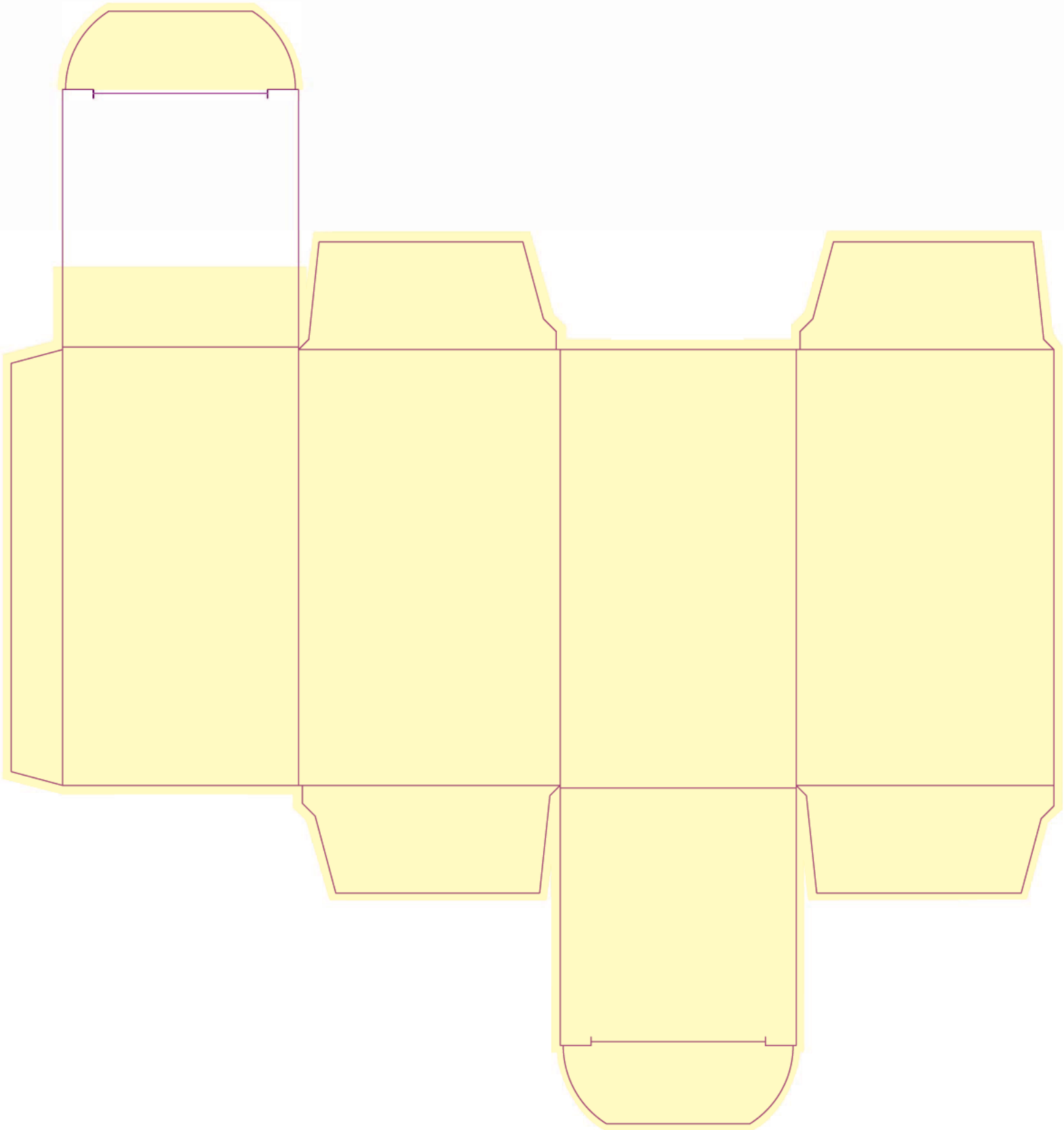
Uptravi® selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 400 mcg US, 60 tablets**	
	Mock up code **UPT-PC-400-US-554**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 400 mcg US, 60 tablets**	
	Mock up code **UPT-PC-400-US-554**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Uptravi selexipag tablets 600 mcg 60 tablets

Lot:

Exp.:

NDC 66215-606-06

Uptravi selexipag tablets

600 mcg

Rx only
60 tablets

Each tablet contains 600 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-600-US-555
46 x 51 x 85
076 A02

NDC 66215-606-06

Uptravi selexipag tablets

600 mcg

Rx only
60 tablets

Uptravi selexipag tablets

Rx only
60 tablets

(b) (4)

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

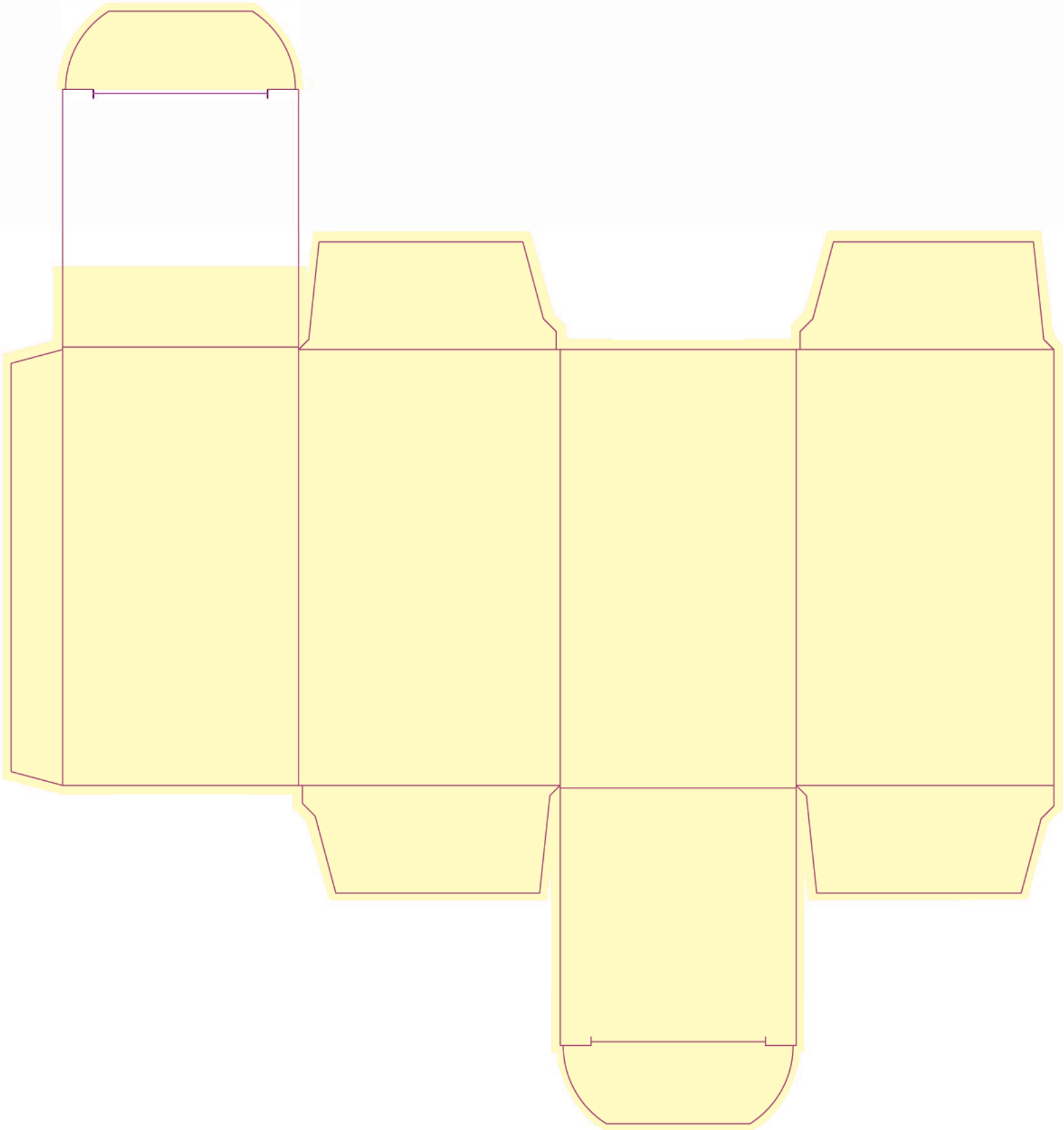
Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 600 mcg US, 60 tablets**	
	Mock up code **UPT-PC-600-US-555**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 600 mcg US, 60 tablets**	
	Mock up code **UPT-PC-600-US-555**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Exp.:

Lot:

Uptravi selexipag tablets 800 mcg 60 tablets

NDC 66215-608-06

Uptravi® selexipag tablets

800 mcg

Rx only
60 tablets

Each tablet contains 800 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-800-US-556
46 x 51 x 85
076 A02

NDC 66215-608-06

Uptravi® selexipag tablets

800 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

N 3 66215 60806 7

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

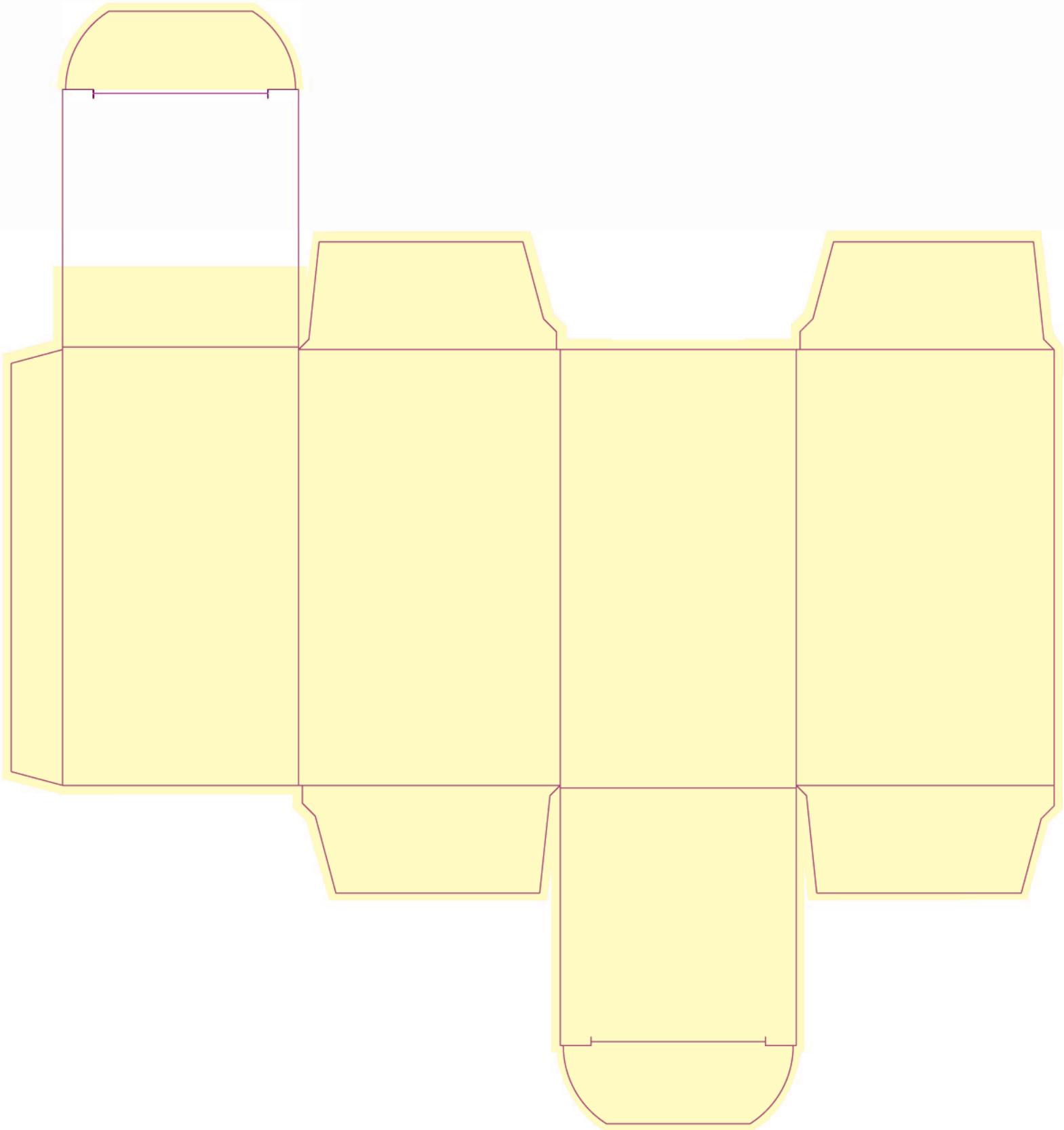
Uptravi® selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 800 mcg US, 60 tablets**	
	Mock up code **UPT-PC-800-US-556**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 800 mcg US, 60 tablets**	
	Mock up code **UPT-PC-800-US-556**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Uptravi selexipag tablets 1000 mcg 60 tablets

Lot:

Exp.:

NDC 66215-610-06

Uptravi selexipag tablets

1000 mcg

Rx only
60 tablets

Each tablet contains 1000 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-1000-US-557
46 x 51 x 85
076 A02

NDC 66215-610-06

Uptravi selexipag tablets

1000 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

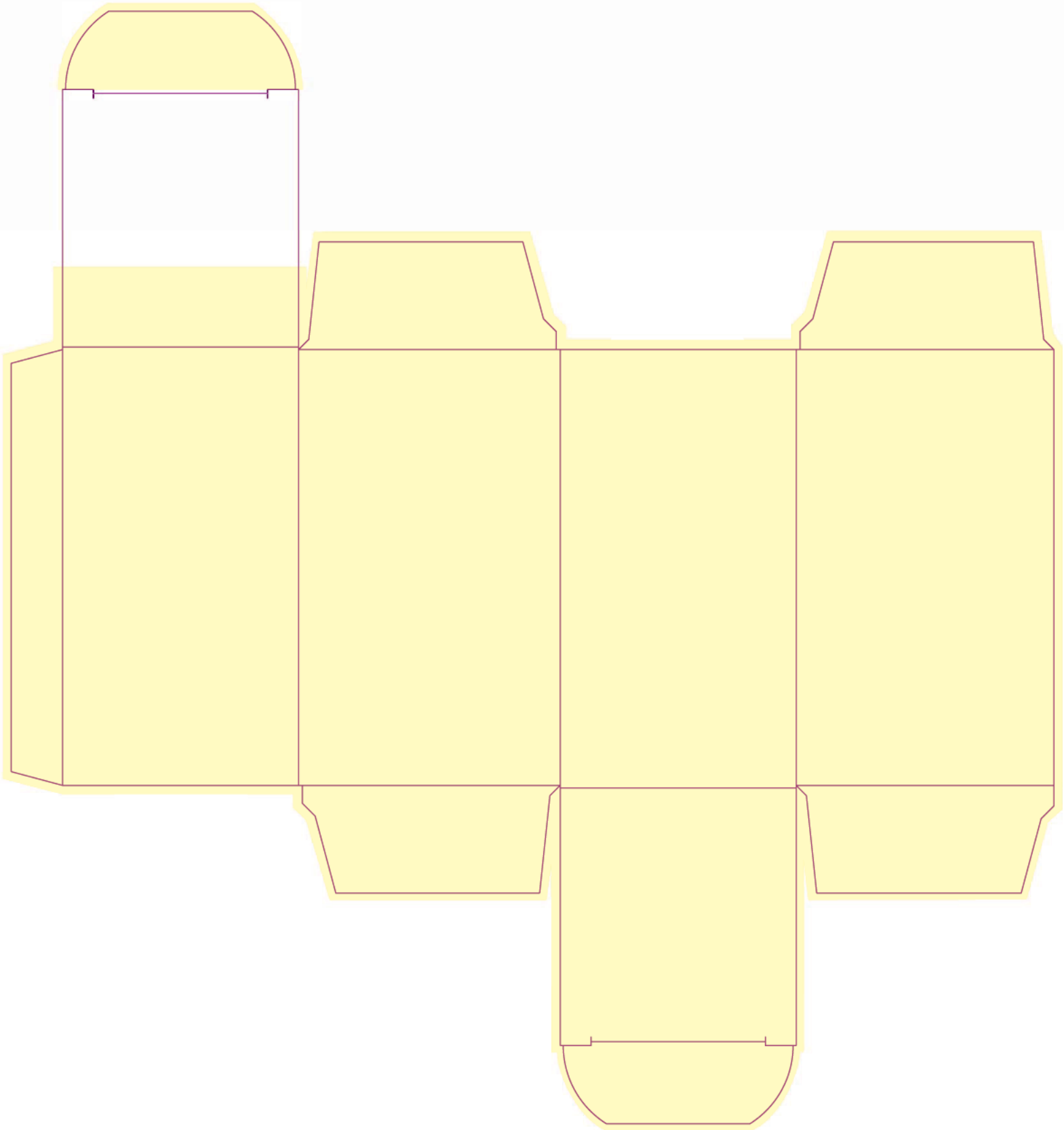
Uptravi selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1000 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1000-US-557**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1000 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1000-US-557**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Exp.:

Lot.:

Uptravi selexipag tablets 1200 mcg 60 tablets

NDC 66215-612-06

Uptravi selexipag tablets

1200 mcg

Rx only
60 tablets

Each tablet contains 1200 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-1200-US-558
46 x 51 x 85
076 A02

NDC 66215-612-06

Uptravi selexipag tablets

1200 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

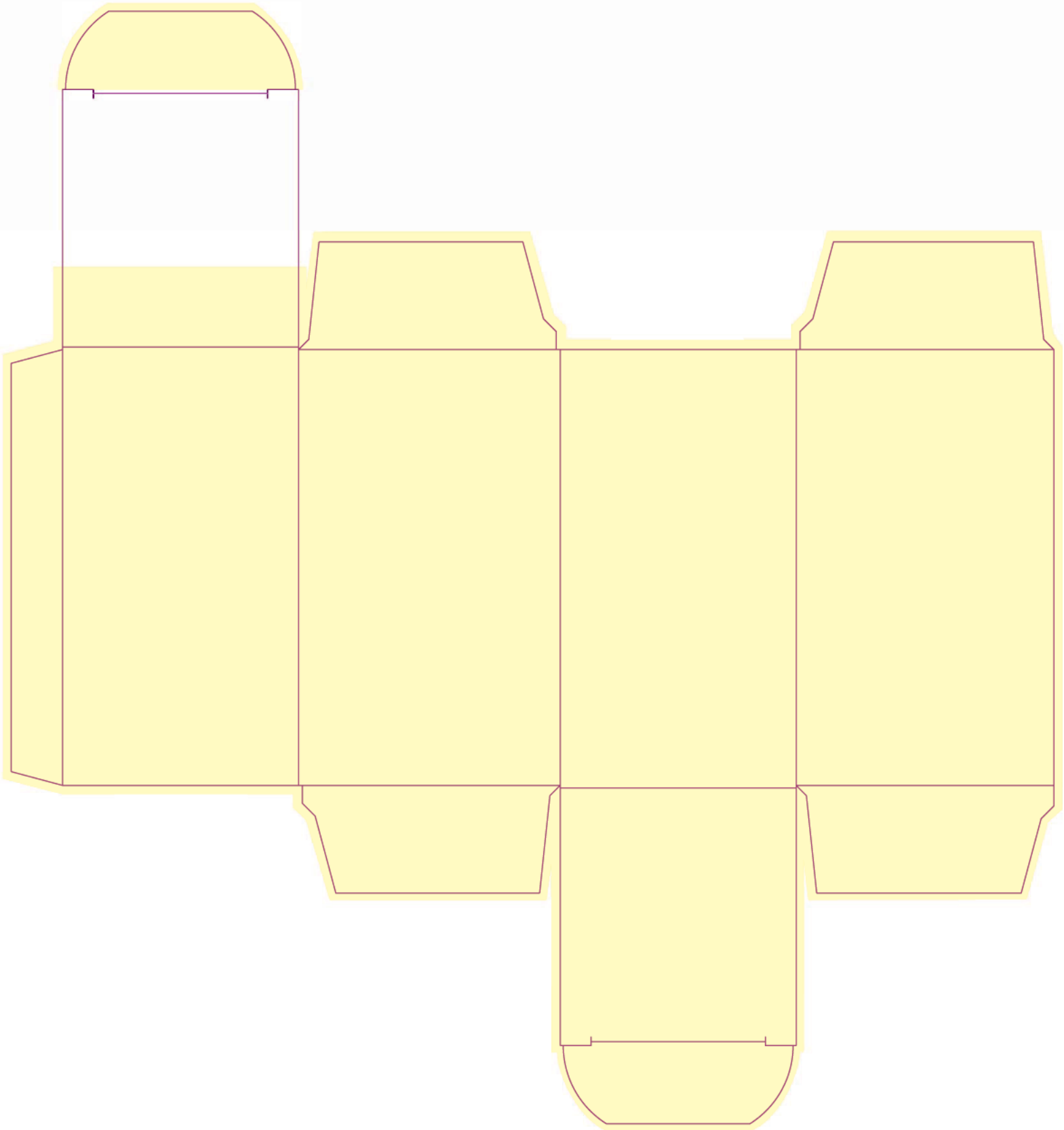
Uptravi selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1200 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1200-US-558**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1200 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1200-US-558**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Exp.:

Lot.:

Uptravi selexipag tablets 1400 mcg 60 tablets

NDC 66215-614-06

Uptravi selexipag tablets

1400 mcg

Rx only
60 tablets

Each tablet contains 1400 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-1400-US-559
46 x 51 x 85
076 A02

NDC 66215-614-06

Uptravi selexipag tablets

1400 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

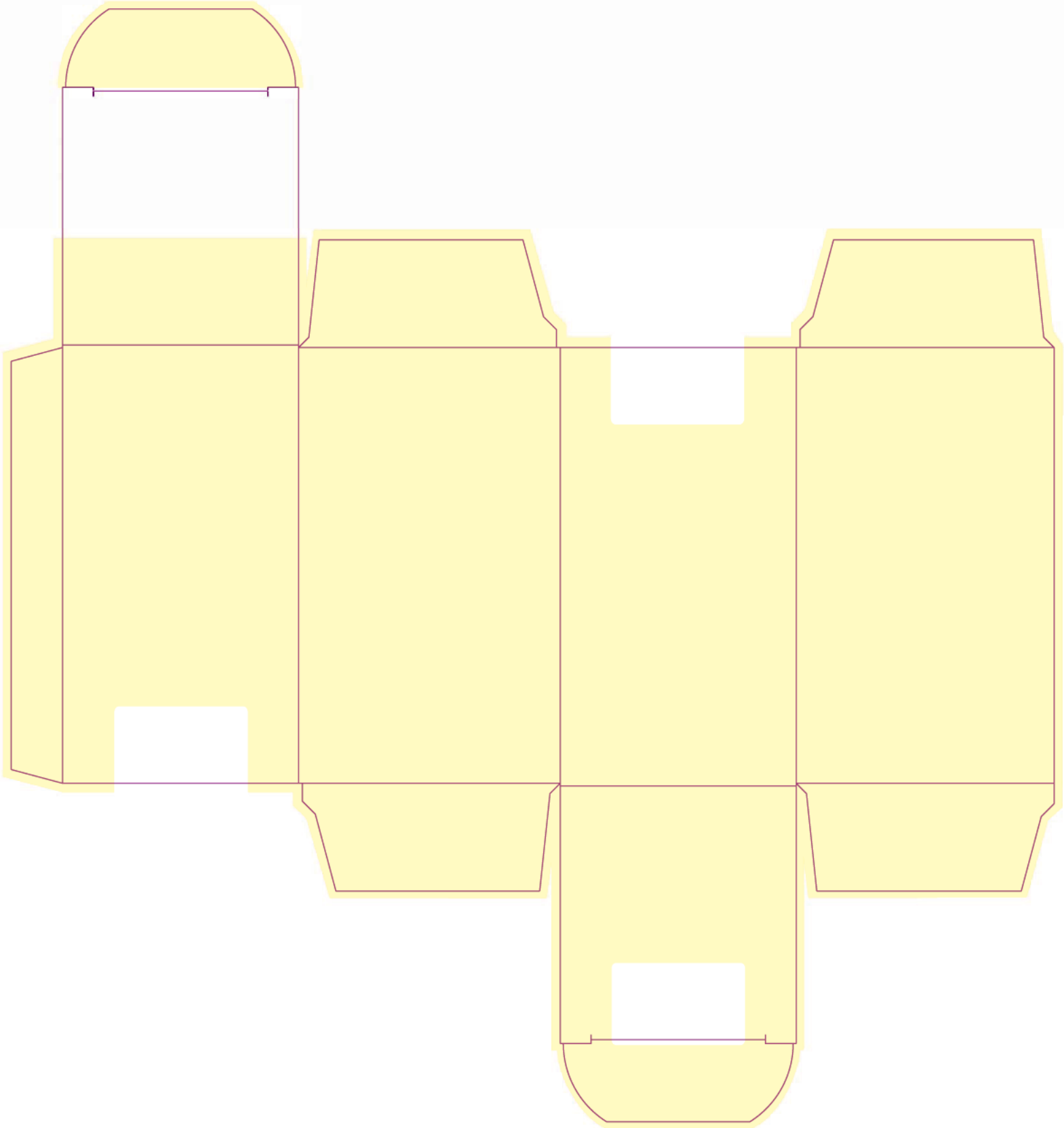
Uptravi selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1400 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1400-US-559**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)



ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1400 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1400-US-559**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

(b) (4)

Exp.:

Lot.:

Uptravi selexipag tablets 1600 mcg 60 tablets

NDC 66215-616-06

Uptravi® selexipag tablets

1600 mcg

Rx only
60 tablets

Each tablet contains 1600 mcg of selexipag.

Read the Prescribing Information before use.

Dosage: see package insert.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP controlled room temperature.]

Keep out of the reach of children.

UPT-PC-1600-US-560
46 x 51 x 85
076 A02

NDC 66215-616-06

Uptravi® selexipag tablets

1600 mcg

Rx only
60 tablets

See top panel for lot number and expiration date.

Patent:
www.actelion.com/patents

N 3 66215 61606 2

Manufactured for:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA 94080 US

Made in the UK

ACTELION

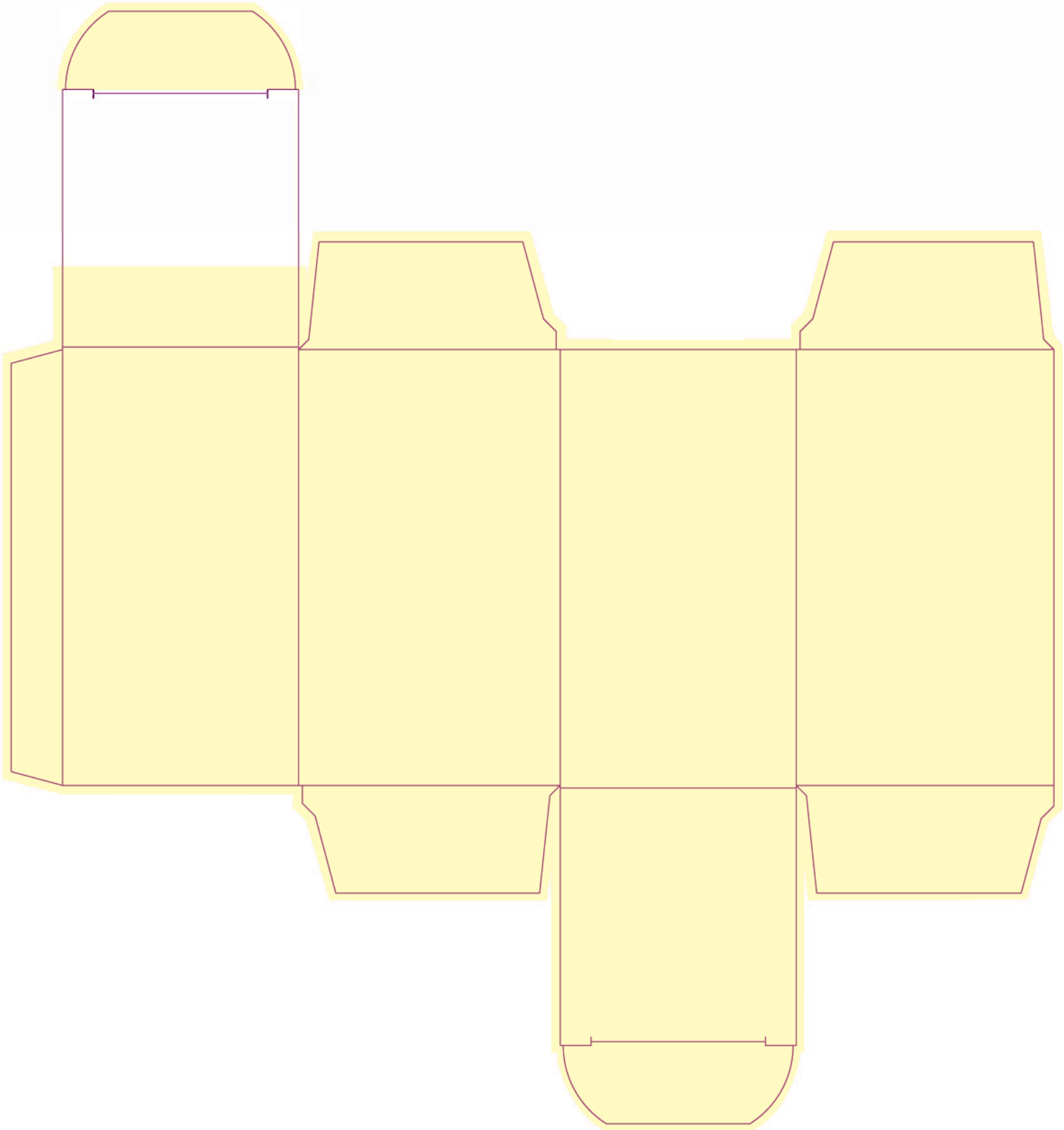
Uptravi® selexipag tablets

Rx only
60 tablets

(b) (4)

ACTELION Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil Switzerland E-mail: top-text_artwork@actelion.com	Product name **Uptravi 1600 mcg US, 60 tablets**	
	Mock up code **UPT-PC-1600-US-560**	Proof no. / date **1 / 17-Mar 2015**
	Dimension **46 x 51 x 93 mm**	Technical drawing no **076 A02**

(b) (4)

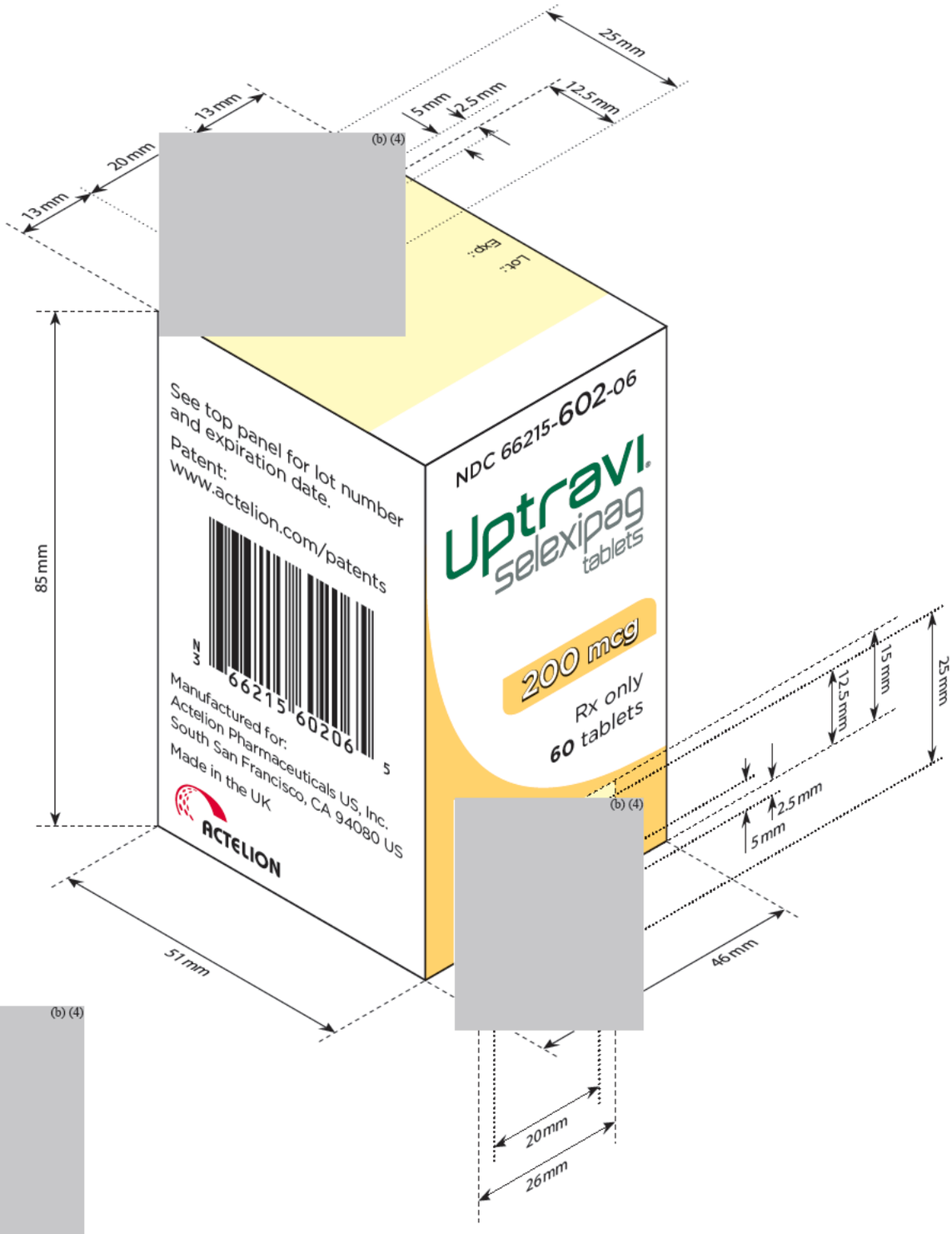


ACTELION

Actelion
Pharmaceuticals Ltd.
Gewerbestrasse 16
CH-4123 Allschwil
Switzerland
E-mail:
top-text_artwork@actelion.com

Product name	
Uptravi 1600 mcg US, 60 tablets	
Mock up code	Proof no. / date
UPT-PC-1600-US-560	**1 / 17-Mar 2015**
Dimension	Technical drawing no
46 x 51 x 93 mm	**076 A02**

(b) (4)



(b) (4)

UPT-PC-200-US-437_3D pp01 indd 1

19.11.14 16:06

(b) (4)

Product	**Uptravi 200 mcg / 60 tablets**		**Actelion Pharmaceuticals Ltd**	1. Proof	(b) (4)
Material No.	**UPT-PC-200-US-437_3D**	**Actelion**		2. Proof	
Replaced No.		Order File	Fontsize **9pt**	3. Proof	
Country	**US**		technical **6,5pt**	4. Proof	
Code No.	**366215602065**	contract manufacturer:	Used Font **Gotham**	5. Proof	
Dimension	**46 x 51 x 85 mm**		**(Book, Medium, Bold)**	6. Proof	
Drawing No.	**076A02**		Colours (b) (4)		(b) (4)
		Page **1** of **1**	(b) (4) **+ Safety Seal**		
Sec. Edge Marks		(b) (4)	additional Die cut, Varnish-free		

Reference ID: 3864143

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
12/21/2015