LVDR:TEAE by Decreasing Frequency to ≥2% in IC351-Treated Patients

Event Classification	IC351 (N = 331)	
	n	%
	144	43.5
Headache	39	11.8
Dyspepsia	35	10.6
Rhinitis	24	7.3
Vasodilatation	17	5.1
Pharyngitis	15	4.5
Back pain	12	3.6
Pain	12	3.6
Surgical procedure	12	3.6
Diarrhea	10	3.0
Dizziness	8	2.4

9.5.5.8.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

There were a total of 19 discontinuations . 9 were due to serious AE's. serious event included a case of vitrous detachment.

9.5.5.8.3 SERIOUS ADVERSE EVENTS

Fourteen patients experienced serious adverse events in this study. No deaths occurred in this study. None of the serious adverse events, in the opinion of the investigator, was considered to be related to the study drug or protocol procedures. Patients 004-1169, 004-1173, and 504-5240 discontinued from the study due to serious adverse events. Table 49 lists the serious adverse events reported during this study.

Table 48: LVDR: Serious Adverse Events: Serious Adverse Events: All Randomized Patients

Medical Officer's Comments:

1. These three open-label studies provide information on the safety and tolerability of IC351 administered long-term.
2. The serious adverse events were mostly unrelated to the study drug. In the popuation studied, the mycardial infarctions and cereberovascular events were related to preexisting condition and the incidence of the events were comparable to the population at large.
3. Of 6 deaths reported, none could be clearly attributed to the study drug.
4. Of note were the discontinuation due to headaches and dyspepsia reported on increased dosing. This further reinforces the concept of 10mg dose as a first option to the patients.
5. The most frequently reported adverse events were headache, dyspepsia, back

pain, infection, and flu syndrome. Myalgia, rhinitis (nasal congestion), and vasodilatation (flushing) were reported less frequently.

6. There were no clinically significant laboratory abnormalities attributable to IC351.

9.5.6 Special Safety Considerations :

9.5.6 .1 EFFECTS OF IC351 ON BLOOD PRESSURE AND HEART RATE:

In the primary placebo-controlled phase 3 integrated database, the mean changes from baseline to endpoint for blood pressure in patients treated with IC351 were not statistically different from those seen in patients treated with placebo. When adverse events were analyzed in patients with and without hypertension treated with either IC351 or placebo, there were no significant differences between the groups.
In the clinical pharmacology populations studied, the effect of IC351 on vital signs in normotensive and hypertensive subjects was independent of dose and of no clinical significance . There were no clinically significant decreases in blood pressure when IC351 was administered alone or co-administered with anti hypertensive medications.

Medical Officers Comments:

The data was reviewed .The above mentioned hemodynamic alterations, did not produce a clinically significant event.

9.5.6.2 PHARMACODYNAMIC INTERACTIONS WITH ANTIHYPERTENSIVE AGENTS

The reader is referred to clinical pharmacology section and a formal review of Drug – Drug interactions.
The potential of IC351 to augment the hypotensive effects of all major antihypertensive classes were examined, including a calcium channel blocker (amlodipine. LVAV and LVDP), an ACE inhibitor (enalapril,.LVBC), a beta blocker (metoprolol, LVAW), a thiazide diuretic (bendrofluazide,.LVAX), an angiotensin II receptor antagonist (any type and dose, combination with thiazide acceptable,.LVDS), and an alpha 1 adrenergic antagonist (tamsulosin,.LVAY).
The primary parameters assessed in all of these studies included systolic blood pressure, diastolic blood pressure, and heart rate, all of which were measured intermittently over a period of at least 12 hours after IC351 administration. These studies indicate that there was no clinically significant interaction between IC351 and any of the classes of anti hypertensive agents examined.
In the primary placebo-controlled phase 3 clinical studies, data were analyzed for the incidence of adverse events in patients taking and not taking concomitant antihypertensive medications . There were no significant differences between the patient groups in the incidence of adverse events.

Medical Officers Comments:

A formal biopharm review was done by the particular division and the reviewer Dr Roy was consulted. IC351-Amoldipine interaction did show some additional hypotensive effect which was clinically insignificant in view of this reviewer.
However some interactions were done with IC 10mg IC 351. These may not be extrapolated to 20mg dose.

Pharmacodynamic Interactions with Organic Nitrates:

The potential for a pharmacodynamic interaction between 10 mg IC351 and organic nitrates was examined in 3 separate studies : LVAB, LVBY, and LVCM.
In these nitrate interaction studies, the greatest augmentation of the hypotensive effects of nitrates was typically seen within 4 hours of IC351 administration. However the effect lasted upto to 30 hours. In these studies the sponsors only used 10 mg dose of IC 351.

Medical Officers Comments:

The additive hypotensive effect of IC 351 on Nitrates is a major clinical concern in drugs of this class. A full evaluation of Nitrate – IC 351 interaction is needed along with the risk management plan.
The concomitant use of nitrate with IC 351 should be contraindicated.

9.5.6 .3 Cardiovascular Adverse Events

9.5.6.3.1 HYPOTENSION, SYNCOPE, AND VASODILATATION (FLUSHING)
According to the sponsor;

1. The clinical pharmacology studies showed that the incidence of postural hypotension and dizziness reported with IC351 treatment were not different from non-IC351 therapy.

2 . Of over 1000 subjects who received IC351 in clinical pharmacology studies, there were 7 subjects who had syncope after IC351 administration . Syncope was likely to have been vasovagal in 4 of these 7 subjects and was assessed as unrelated to study drug. Of these, three events occurred after venous cannulation, one event occurred during an eye examination, and one event occurred 2 days and 10 hours after dosing. In the remaining 3 subjects, the syncope occurred in subjects who took nitrates with IC351 during the comparative study LVCM with sildenafil of nitrate interactions. These episodes were due to postural hypotension following nitrate administration, although an augmentation of the blood pressure decrease by IC351 could not be ruled out. Two subjects who took nitrates and IC351 during the comparative study LVCM between IC351 and sildenafil also experienced syncope. Thus the cases of syncope that occurred in IC351-treated subjects were either vasovagal and not assessed as related

to study drug or seen in subjects who received organic nitrates concomitantly with IC351.

3)In the primary placebo-controlled phase 3 studies, there were no reports of hypotension or postural hypotension in IC351-treated patients compared with 1 occurrence of hypotension and 1 occurrence of postural hypotension in placebo-treated patients. There was one report of syncope in IC351-treated patients (event occurred in study LVDJ in patient 018-1851 who had a prior history of syncope, 2 days after the prior dose of IC351 and after 3 alcoholic drinks) and 2 reports of syncope in placebo-treated patients. None of these events were considered related to study drug. In all phase 2 and phase 3 studies, including the open-label studies, there were 2 reports of syncope in IC351-treated patients (studies LVDJ and LVBL) compared with 3 reports of syncope in placebo-treated patients (studies LVBJ and LVCQ) None of these events are assessed as related to study drug by the Sponsor.

In clinical pharmacology studies, the incidence of vasodilatation (flushing) was 5.6% in subjects who received IC351 and 4.8% in subjects who received placebo. In the primary placebo-controlled phase 3 studies, the incidence of flushing was 3.7 % for all IC351-treated patients compared to 1.6 % for placebo-treated patients.

Medical Officers Comments:

- The combination of Nitrates and IC351 has significant hypotensive effect. The incidence of dizziness and syncope was also higher in the Nitrate interaction studies.
- Vasodilation is an inherent mechanism of this drug. There should be a warning about the additive effects other vasodilator drugs (amoldipine , alcohol) when given with IC351.
- Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebro vascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in association with the use of another agent in this class. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity. So an extreme caution needs to be used in patients with risk of heart disease and these agents.

9.5.6.3. 2 ANGINA PECTORIS:

9 patients of angina pectoris were reported across IC 351 studies . 2 patients were in Patients in study LVBY, a drug-interaction study of IC351 with organic nitrates. All of them had a history and risk factor for this disease and investigators assessed the events to be unrelated to the drug.

Medical Officers Comments:

The data review did not causally link IC 351 to the occurence of angina pectoris in the studied population.

9.5.6.3.3 MYOCARDIAL INFARCTION AND CARDIAC MORTALITY:

Based upon the age and co-morbid conditions of the patients in the phase 2 and 3 trials, some cases of serious cardiovascular adverse events, including myocardial infarction, would be expected in the population of over 4000 patients studied.
Across all IC351 double-blind studies, there was one report of myocardial infarction inIC351-treated patients (study LVAC) and 3 reports of myocardial infarction in patients who did not take IC351: 2 in placebo-treated patients (study LVBK, LVCO) and 1 inpatient 117-9703 in study LVBK who was randomized to IC351, but who experienced a myocardial infarction prior to taking any study medication . In the two open-label long term safety studies, there were 9 reports of myocardial infarction, all of which occurred in study LVBL. Overall, there were 10 reports of myocardial infarction in patients taking IC351, or less than 0.65 per 100 patient-years, compared with 1.1 per 100 patient-years in patients who received placebo.
Overall, there were seven deaths reported in IC351 trials. Of these, four deaths were assessed as cardiac deaths. All the patients in this group had underlying cardiac condition and associated risk factors for the disease.

Medical Officers Comments:

1. The myocardial infarction rate in open label studies as well as the combined data on phase III studies shows comparability with placebo subjects and the rate in population at large.

2. The data submitted on MI's and cardiac mortality , is comparable with another drug in its class as well as general population. Upon review of the cases these serious events could not be directly attributed to the drug.

9.5.6.3.4 CONGESTIVE HEART FAILURE OR ARRHYTHMIA AND CEREBROVASCULAR EVENTS:

Cardiac events were reported in these categories. All were unrelated to IC 351 as assessed by the investigators.

Medical Officers Comments:

This reviewer could not unequivocally attribute these cardio vascular events to IC 351.

9.5.6.3.5 ELECTROCARDIOGRAMS

Electrocardiograms were obtained at screening and at final visit for the studies comprising this database except for LVCQ for which ECG will be obtained at the 6

month final visit. There were no significant differences in mean change from baseline to endpoint among the treatment groups for average heart rate, PR interval, QRS interval, QTc interval, and QT interval . There were no significant differences among treatment groups for a change from normal to abnormal ECGs over the course of the studies for the following parameters: axis abnormality, conduction disturbance, ischemia, morphology, myocardial infarction, supraventricular rhythm, ventricular rhythm, ST segment abnormality, or T wave abnormality . Under "other rhythm" parameters, there was a statistically significant difference among treatment groups, with the 2.5 mg IC351 group showing a higher rate of change of 29.1% from normal to abnormal compared with a lowest rate of change of 10.2% for the 20 mg IC351 group. The change for this "other rhythm" parameter for placebo was 17.4% and for all IC351-treated patients was 16.4%. This difference was not considered to be clinically significant.

Medical officer's comments:

- Clinically significant changes in electrocardiogram findings in IC351-treated patients vs placebo were not demonstrated .
- The data reviewed showed no unusual trends in QTc with the use of IC 351. However these studies tested 40mg as their highest dose.
- A cardio renal consult was done that essentially concluded that at a proposed 20mg marketing dose the safety margin (40mg max dose in Qt studies) was narrow for the QTc data submitted . From the submitted data there was no signal for QTc prolongation in the doses tested. However since the sponsor seeks only 20mg dose more studies are required to widen the safety margin.
- This makes a case for not approving 20mg at present .

9.5.6.4 Visual Adverse Events:

According to the sponsor , In clinical pharmacology and phase 2 and phase 3 studies of more than 4000 subjects who took IC351, no dose-related visual symptoms, especially of color tinge changes, occurred with multiple doses of 100 mg for 21 days (study LVBG) and single doses up to500 mg. There were three reports of abnormal color vision in the 4000 patients treated with IC351 (a rate <0.1%).

One healthy subject in the clinical pharmacology study LVCN (subject 48, 20 mg IC351)reported a single episode of chromatopsia (reported as blue vision) without anyabnormality in the Farnsworth-Munsell (FM) 100-hue test. Patient 212-6207 in the phase 3 study LVBN who had previously experienced a blue tinge to vision consistently after each dose while being treated with sildenafil, reported "visual field defect", described as visual color disturbance with red objects appearing blue and blue and yellow objects appearing orange following the 40th dose of 10 mg IC351; he took 13

more doses without chromatopsia occurring. A participant in the open-label study LVBL reported blue vision (patient 422-1361, 20 mg IC351).The primary placebo-controlled phase 3 database was examined for all COSTART event terms concerning vision (abnormal vision, amblyopia, and visual field defect) and the actual event terms for these cases were examined . In the combined IC351 group, 8 of 949 (0.8%) had at least one visual adverse event versus 5 of 379 (1.3%) in the placebo group.

Medical Officers Comments:

Color vision abnormalities were (<0.1%) .See medical Officers comments following ocular adverse events.

9.5.6.4.1OCULAR ADVERSE EVENTS:

In the earlier phase 2 studies LVBF, LVBG, and LVAC, a small number of patients reported ocular symptoms – swelling of eyelids, sensations described as eye pain or pressure, and conjunctival hyperemia – for which a plausible relationship to IC351 could not be excluded. The primary placebo-controlled phase 3 database was specifically examined for these events (conjunctivitis, eye hemorrhage, eye pain, and face edema). In the combined IC351 group, 20 of 949 (2.1%) had at least one ocular event versus 5 of 379 (1.3%) in the placebo group .

Swelling of eyelids occurred in 3 of 949 (0.3%) patients who received IC351 and in 1 of 379 (0.3%) patients who received placebo. All these events in the IC351 group were assessed as mild. A case of swollen lips (patient 502-5103 in study LVCQ) and a case of swelling of the face (patient 804-4217 in study LVCO) were omitted from this analysis.

In the IC351-treated group, 4 of 949 (0.4%) reported eye pain or pressure (coded to COSTART term "eye pain"). The sensations described as eye pain or pressure was mild in 3 of 4 patients and moderate in one patient. This event was not reported by any patient taking placebo. Events reported in actual terms as redness of eyes (conjunctival hyperemia) were coded to the COSTART term "conjunctivitis." In all IC351-treated patients, 9 of 949 (1.0%) had an event of conjunctivitis (as preferred term) versus 4 of 379 (1.1%) for placebo-treated patients. Of the 9 IC351-treated patients reporting conjunctivitis as preferred term, 4 had conjunctivitis as actual term compared with 4 for placebo-treated patients. In addition, 4 of the IC351-treated patients reported redness of eyes as actual term whereas none of the placebo-treated patients reported redness of eyes. All instances of redness of eyes were mild. One IC351-treated patient had an event of eye irritation which was reported as mild in severity.

Medical Officers Comments:

These mild to moderate ocular events occurred at a low rate across the studies. An opthalomology consult was obtained and the consultant opined that there was no difference in this product and another drug of its class as far as the vision abnormalties were concerned and wanted the label to reflect that. There were many deficiencies in the studies submitted for review.

He further recommended that additional adequate and well-controlled studies will be are required .

9.5.6.5 Studies of Sperm Function and Semen

Study LVCD (N=204) and LVCZ(N=217)

The demographic and baseline characteristics did not differ significantly between the two treatment groups. Specific characteristics included height, weight, vital sign measurements, current smoking habits, and current alcohol consumption. These studies were conducted in the US.

The mean age of subjects was 51.1 years in the 10 mg IC351 group and 51.8 years in the placebo group. The majority of subjects were Caucasian, accounting for 91.3% and90.1% of subjects in the 10 mg IC351 and placebo groups, respectively. There was no significant difference between the treatment groups with regard to baseline (Visit 1) semen characteristics. At baseline, the mean sperm concentration was 73.4 x 10 6 /mL and 80.3 x 10 6 /mL for the 10 mg IC351 and placebo groups, respectively.

Baseline mean sperm motility was 60.4% and 61.4% for the 10 mg IC351 and placebo groups, respectively. Baseline mean normal sperm morphology was 59.6% and 58.4% for the 10 mg IC351 and placebo groups, respectively. The mean number of sperm per ejaculate at baseline was 214.7 x 10 6 and 227.1 x 10 6 for the 10 mg IC351 and placebo groups, respectively.

A second study LVCZ(N=217) was under taken to see the effect of 20 mg on semen parameters. It was a 6-month, double blind, placebo-controlled study in healthy men and men with mild erectile dysfunction to assess the effect of daily dosing (for 6 month) of 20 mg of IC351 on semen parameters. This study was done in 18 Centers in the US. 217 healthy Males of ages 40- 70 enrolled.

Medical Officers Comments:

- The reviewer did not find a clinically significant effect of IC 351 on the semen parameters (semen volume, sperm concentration, sperm motility and morphology) of patients treated with IC 351.
- The most frequent adverse events observed in subjects treated with 10/20 mg IC351 were headache, dyspepsia, and back pain. These occurred at a slightly higher rate than reported in the overall data base. The clinical significance of this

is unclear. There were no deaths reported. There were no serious adverse events directly attributable to the drug.

9.5.6.6 Clinical Laboratory Evaluation

9.5.6.6.1 SERUM CHEMISTRY

There were no consistent clinically significant findings related to serum chemistry tests in the IC351-treated patients when mean changes from baseline to end point and when treatment emergent high or low abnormal values were analyzed . There were small but statistically significant differences among treatment groups and between placebo and IC351 treated groups in some serum chemistry parameters for mean changes from baseline to endpoint (AST, ALT, alkaline phosphatase, total protein, and albumin). None of these changes were clinically significant. Similar clinically insignificant but statistically significant differences between placebo and IC351 groups were also seen for treatment emergent high or low values for serum urea nitrogen, and serum chloride.

9.5.6.6.2 LIVER ENZYME ELEVATIONS :

IC351 database was analyzed for reports of liver enzyme elevations of more than 3 times the upper limit of normal for serum ALT and serum AST in all patients who received IC351 for more than 2 weeks. A total of 2693 IC351-treated patients and 870 placebo-treated patients were included in this overall analysis.There were no instances of elevations of serum ALT or AST to more than 3X the upper limit of normal during treatment in these early studies.

In patients who received IC351 for more than 2 weeks, there were none who fulfilled the criteria for "Hy's Law" (the occurrence of elevations of serum ALT or serum AST to more than 3 times the upper limit of normal in combination with an elevation of serum bilirubin to more than 1.5 times the upper limit of normal without evidence of biliary obstruction). There were, however, 2 patients who had elevations of serum transaminases to more than 3X the upper limit of normal with hyperbilirubinemias, but in both these patients, the liver enzymes elevations were from identifiable causes other than study drug. TABLE 49

Table 49:Liver enzyme elevations IC 351 Treated Patients:(source Table ISS.8.3.)

Table49	Liver Enzyme Elevations in IC351-Treated Patients

Number	Study	Patient#	Dose	Serum ALT or AST Elevations				Confounding factors
				>3X	>5X	>10X	>20X	
1	LVAC	002-1216	10 mg	ALT, AST	AST, ALT	AST	No	Alcohol[a]
2	LVBN	216-6626	10 mg	ALT	No	No	No	Cholelithiasis
3	LVCD	300-1000	10 mg	AST	AST	No	No	Alcohol
4	LVCD	322-1237	10 mg	AST	AST	No	No	Alcohol
5	LVCE	017-3812	2.5 mg	ALT, AST	ALT	No	No	ERCP, cholelithiasis
6	LVCO	803-4168	20 mg	ALT	No	No	No	Hepatitis B
7	LVCO	805-4269	10 mg	ALT, AST	No	No	No	Hepatitis C
8	LVCQ	501-5056	20 mg	ALT	No	No	No	Alcohol
9	LVCQ	504-5236	20 mg	ALT	ALT	No	No	Alcohol
10	LVDJ	009-1401	20 mg	ALT, AST	No	No	No	Alcohol
11	LVBO	422-4660	Titration	AST	No	No	No	Past history of alcohol abuse; abnormal bilirubin at study entry
12	LVBR	333-3406	20 mg	ALT	ALT	No	No	None
13	LVCK	328-2385	20 mg	ALT	No	No	No	Febrile illness, fatty liver on ultrasound, amoxicillin
14	LVBD	002-23	Titration	ALT	No	No	No	Alcohol
15	LVBD	003-6	Titration	ALT	No	No	No	None
16	LVBL	111-2229	Titration	ALT AST	No	No	No	Prior history of ethanol
17	LVBL	211-3154	Titration	AST	No	No	No	Alcohol, poorly Controlled.DM
18	LVBL	411-1097	Titration	ALT, AST	ALT	ALT	No	None

[a] Alcohol, a history of excessive alcohol intake

9.5.6.6.3 HEMATOLOGY

There were no consistent clinically significant events related to hematology tests in theIC351-treated patients. None of the hematology parameters showed differences in mean change from baseline to endpoint among treatment groups . There were no instances of neutropenia or thrombocytopenia attributable to IC351.

9.5.6.6.4 URINALYSIS

The sponsors analysis showed no statistically or clinically significant changes in urinalysis tests among treatment groups.

Medical officer's comments:

1. A review of Lab tables and these patients' clinical outcomes revealed no irregular or outstanding clinical adverse events. Thus, while these lab values may be "markedly" elevated, they did not appear to translate into meaningful clinical adverse outcome. In addition, the incidence of such lab values waslow. Finally, these lab values might reflect the effects of other illnesses or background variables.
2. The data submitted describing "shifts" in laboratory values to (a) values below the lower limit of the normal range ("shift to low") or (b) to values above the upper limit of the normal range ("shift to high") were not notable for any corresponding clinically important drug-related changes.
3. Overall, all available laboratory data do not raise concerns about significant drug-induced Lab toxicity associated with the use of the CIALIS™ .

9.5.7 Adverse events by age, concommitent medications (anti hypertensives),hypertension and Diabetes melitus.

9.5.7.1 AGE

Patient Age Greater Than 65 Years

According to the sponsor, For IC351-treated patients, 55.5% of patients >65 years of age had at least one treatment-emergent adverse event versus 57.5% of patients ≤65 years of age. A similar pattern occurred for placebo-treated patients (45.8% of patients >65 years of age had at least one treatment-emergent adverse event versus 48.4% of patients ≤65 years of age).

Medical Officers Comments:

The clinical pharmacology studies showed >25% exposure in patients >65years of age These patients reported dose related higher incidence of back pain and myalgia .This was Particularly notable in patients with impaired renal function. The lwer doses (5,10mg) may have a better safety profile.

9.5.7. 2 Patients Taking Concomitant Antihypertensive Medications

The incidence of adverse events was similar in IC351-treated patients who were taking concomitant anti hypertensive medications and patients who were not.

9.5.7.3 Patients with Hypertension

The sponsor did a subgroup analysis and found that the incidence of adverse events was similar in IC351-treated patients with and without hypertension.

9.5.7.4 Patients with Diabetes Mellitus

The sponsor did a subgroup analysis and found that the incidence of adverse events was similar in IC351-treated patients with and without diabetes mellitus.

Medical officer's comment:

- The incidence of adverse events was similar in IC351-treated patients who were concomitantly taking antihypertensive medications and patients who were not.
- The incidence of adverse events was not increased in patients with hypertension or diabetes mellitus in IC351-treated group however of note is the fact that in subjects with diabetes drug exposure was 19% lower than in healthy subjects matched for gender and age. The Diabetic patients (in study LVBK) with orthostatic changes at screening were excluded .This would further lower the adverse event rate. IN diabetic patients3, t1/2 was approximately 3 hours shorter.

9.6 Safety consultations

1. Statistical consult was done for review of statistical methods used and review and analysis of efficacy and safety data.
2. Cardio renal consult was done for a review of Data on QTc.
3. Opthalamology consult was done to review visual safety 3of Cialis ™

9.7 Safety findings and proposed labeling

The current safety data lowers the therapeutic index of Cialis ™ (20mg) to non approval. In this reviewers view the starting dose should be 5 OR 10 mg for most patients with an option to titrate the dose up. If the lower doses are sought;
The label will need revisions to accomplish the following objectives:

1. Convey accurately the PK/PD issues.
2. Convey accurately the efficacy issues.
3. Convey accurately the safety issues.
4. Precautions and warning sections on special populations.
5. Drug-Drug interactions (Nitrates and CYP3A4 inhibitors).

10. Package insert

The proposed package insert was reviewed in great detail. However, at this point the 20 mg dose is not approvable.

11. Use in special populations

Geriatric : Of the total number of patients in the primary efficacy and safety studies of tadalafil, 27% were age 65 and over. Healthy elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years.

Pediatric : Tadalafil has **not** been evaluated in individuals less than 18 years old.

Hepatic Insufficiency : Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) was comparable to exposure in healthy subjects. dose adjustment may be required in severe patients.

Renal Insufficiency : In subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment, tadalafil exposure (AUC) was higher than in healthy subjects as shown in a clinical pharmacology study. Additionally the main metabolite had prolongation of t ½ to 55 hours causing higher adverse events. This group of patients need a lower starting dose (5 MG) . Tadalafil has not been studied in subjects with severe renal impairment (creatinine clearance ≤30 mL/min) and should be contraindicated in these patients.

Patients with Diabetes : Tadalafil exposure (AUC) in patients with diabetes was approximately 19% lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

Pregnancy, Nursing Mothers and Pediatric Use: CIALIS is not indicated for use in newborns, children or women.

12. Conclusions and recommendations

12.1. Overall risk/benefit assessment

The reader is also referred to the Executive Summary section of this review.
Benefits:

IC351 (tadalafil) is a inhibitor of the cGMP-specific phosphodiesterase type 5 (PDE5). Following sexual stimulation , the local release of nitric oxide with activation of guanylyl cyclase, inhibition of PDE5 by IC351 produces increased levels of cGMP in the corpus cavernosum . This results in smooth muscle relaxation and in flow of blood into the penile tissues, thereby producing an erection. The pharmacokinetic profile of IC351 showed that it has a mean half-life of 17.5 hours and the mean maximum observed plasma concentration (Cmax) is achieved at a mediantime of 2 hours after dosing.

For estabilishing efficacy of IC351, the sponsors conducted six adequate (N=1328), well-controlled, multi center clinical studies in Argentina, Australia, Canada, Mexico, Spain, and Taiwan. One of these studies included only patients with diabetes mellitus. In addition the sponsor conducted open label studies for long term safety and efficacy in over 1000 patients in conformance with the ICH guidelines. These studies included a broad Spectrum of ED patients
Each primary efficacy study had three co primary endpoints: the IIEF Erectile Function (EF) Domain, SEP Question 2 (assessing the ability to penetrate the partner's vagina), and SEP Question 3 (assessing the ability to maintain the erection). All endpoints were analyzed as the change from baseline. The sponsor was able to show clinically and statistically significant efficacy of 10 mg and 20 mg doses when compared with placebo for the pre defined primary and secondary end points. 10 mg was comparable to the 20 mg dose in its efficacy. 5 mg dose was efficacious in a large number of patients studied and was clinically effective however it failed marginally to show significance in one primary variable (p .064) but was significant in the other two.

Risks:

Tadalafil has a long ½ half life of 17 ½ hours. Frequent treatment related adverse events include among others; headache , dyspepsia , back pain , myalgia , nasal congestion , and flushing . The association of these adverse events with IC351 and of PDE5 inhibitors in general is plausible, however the pathogenesis of myalgia and back pain is yet undetermined and during the trials these events were seen in higher incidence in subjects with diminished renal function and elderly. There was a dose related higher clinical but not a statistically significant events of headache, dyspepsia and vasodilatation reported in some studies.
Adverse events are generally mild to moderate in intensity but with some exceptions. Discontinuations due to adverse events in two long-term, open-label studies, LVBD, LVBL and LVDR were 4.4%, 5.4% and 5.7 % respectively.

Drug Interactions:

In vitro studies: Tadalafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4. So , inhibitors of these iso -enzymes may reduce its clearance.

In vivo studies: showed the following;

- Reduction in IC 351 clearance when it was co administered with CYP3A4 inhibitors such as ketoconazole. In the presence of ketoconazole, geometric mean CL/F was decreased by approximately 50%, which is reflected in an increase in geometric mean half-life, 30.4 hours compared to 15.9 hours when tadalafil was administered alone.

- When Cialis oral was coadministered with amlodipine, to hypertensive patients, the mean additional reduction on supine blood pressure was 7 mmHg systolic and 4 mmHg diastolic was noted when compared with placebo+ IC 351.

- Cialis (20 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers. A small study with 10 mg did show some hemodynamic changes in 25% of the patients.
- IC 351 10mg did potentiate the hypotensive effect of Nitrates. Some interaction questions are unanswered at this time.

Cardiovascular Safety

PDE V inhibitors relax the vascular smooth muscle with resultant vasodilatation. This, in and of itself may be fine in patients with coronary disease who don't take any additional nitrates or coronary vasodilators. It is well known that the agents of this class can cause an additional hypotensive effects with co administration of nitrates. So the co administration of these agents is contraindicated with patients on nitrates or who may require nitrates because of their coronary conditions. The data is still needed to fully under stand the qualitative and quantitative synergies of hypotensive actions of nitrates and cialis for the entire exposure time for cialis since it has a long half life . The sponsors did a study that showed the hypotensive properties at Cmax levels of NTG and Cialis (10mg). There was approximately 20 mm (sysytolic) hypotension with nitrates alone and a 2-5 mm of further augment in hypotensive effect was seen with addition of Cialis™ 10mg. This information will help the patients who are on IC 351 and might require nitrate in a hospital situation but it will still be necessary to know when exactly would it be safe to give, for example , a sub lingual nitrate, in a out of hospital situation if the patient gets an angina or a coronary compromise.

Based upon pre clinical in vivo studies and later phase 1 & 3 studies , the data with 40 mg as a highest tested dose did not clearly suggest that IC351 prolongs the QT interval. However a wider safety margin is required if 20mg is the only dose sought. In the primary, placebo-controlled Phase 3 safety database, 3 patients suffered myocardial infarctions. Two events occurred in placebo-group. The rate of myocardial infarction in patients treated with IC351 was similar to the incidence rate (0.6 per 100 patient-years) observed in an age-standardized general male population. However 9 myocardial infarctions (0.65%) were reported in open label long term study.

Clinical pharmacology data demonstrated that ; Dizziness occurred in 2.4% of patients taking IC351 compared with 1.9% of placebo-treated patients. Syncope occurred in 0.1% of patients taking IC351 compared with 0.5% of placebo-treated patients. Many of these events occurred in Nitrate interaction studies.

Human Sperm Characteristics and Spermatogenesis
LVCD and LVCZ were randomized, double-blind placebo-controlled 6-month studies to evaluate the effect of 10 mg (LVCD) and 20 mg IC351 (LVCZ) given daily did not show clinically significant effect on semen parameters with these doses. However the rate of commonly seen adverse events was higher in these studies when compared to the

placebo controlled data.

Visual Safety

In clinical pharmacology, Phase 2, and Phase 3 studies of more than 4000 subjects who have taken IC351, no dose-related visual symptoms, especially of color tinge changes. There have only been three reports of abnormal color vision in the 4000 patients treated with IC351 (incidence rate <0.1%). The study population showed low incidence of visual abnormalities with this product. The opthalmology consultant report concluded that there was no difference in the vision related effects between this product and sildenafil or placebo.

Laboratory Safety

There were no consistent clinically significant events related to serum chemistry or hematology testing during the clinical program.

In summary, based on safety and efficacy information submitted in NDA 21-368, this reviewer believes that Cialis ™ in the doses tested ;5mg(In many patients),10mg and 20 mg , is effective. However there are some safety issues to be resolved particularly those with the use of nitrates, use in compromised renal function, QTc data and elderly patients. Therefore 20mg dose is recommended for non approval at the present time . This reviewer also believes that 5mg and 10 mg should be the starting dose for this drug. This gives patients and prescribers an option for up titration if needed.

Approvability Issues :

1. Both 10mg and 20 mg showed clinically and statistically significant efficacy. 5 mg was also largely effective. Therefore the patients must be offered an option to start at a lower dose (5 or10mg) with a flexibility of up titration if necessary for the proposed indication of male erectile dysfunction.

2. The AUC of 5mg dose may be doubled in patients with moderate renal impairment. This should be the starting dose for this group of patients.

3.

4.

The following labeling issues will arise if the sponsor chooses to seek 5 and 10 mg as starting dose :

1. The concommittent use of this drug with Nitrates should be contraindicated.
2.
3. Patient population with compromised renal function, particularly the elderly folks should be warned in the label that they may experience higher rate of adverse events like Backpain and myalgias. Dose should reduced in these patients.
4. Patient population who were excluded from IC351 studies should be warned in the label regarding a potential for adverse events
5. Patient population should be warned in the label regarding a potential of adverse events with CYP 3A4 inhibitors like cimetidine, ketoconazole etc.
6. The label should include the warning regarding the drugs potential for visual abnormalities. The sponsors should do an adequate and well controlled trial to clearly define this drugs potential for visual adverse events.
7. The prescribers and the patient must be warned about the potential interaction with the drugs not studied for interactions or studied with a lower dose of IC 351 (5,10mg) than the proposed marketing dose.
8. The potential for long half life related interactions (including the increased exposure to main metabolite) and its potential for adverse events should be included in the label. These include myalgia and back pain. The mechanism of these events is not known and it should be considered as unknown safety risk with this drug.

The risk benefit ratio of this drug particularly with 5mg and 10mg as a starting doses, lends itself to the starting dose at present time. I think the sponsors should obtain nitrates and other safety related related data before exposing this drug to general public

.

12.2. Recommendations

It is the view of this reviewer that the 20mg formulations of Cialis™ be given a NOT approvable action for the proposed indication of *" male erectile dysfunction", pending*

resolution of additional safety related data as detailed in the previous sections .

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

/s/

Ashok Batra
4/25/02 05:24:28 PM
MEDICAL OFFICER

Mark S. Hirsch
4/29/02 03:47:38 PM
MEDICAL OFFICER
For some additional comments, please see my memo.

Medical Officer's Review of NDA 21-368
Ophthalmology Consultation

NDA 21-368
Ophthalmology Consult
IND 54,553

Submission date: 6/28/01

Review date: 3/17/02

Sponsor: Lilly Icos LLC
1209 Orange Street
Wilmington, DE 19801
(317) 277-3799

Contact: Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs
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Drug Product: Cialis (tadalafil tablets) 20 mg oral
IC351 (LY450190)

Pharmacologic Category: PDE 5 Inhibitor

Proposed Indication: Erectile dysfunction

Background:

Phosphodiesterase inhibitors have the potential to affect visual function. The mechanism is believed to involve the inhibition of PDE6, an enzyme found in the retina and thought to be responsible for phototransduction. The administration of Viagra (sildenafil tablets) has demonstrated dose dependent changes in visual perception and changes in Farnsworth-Munsell 100 hue testing and ERG testing.

Reviewed: Electronic Submission
- Clinical Studies
  - H6D-EW-LVAN
  - H6D-EW-LVCN
- Proposed package insert labeling
- Integrated Summary of Safety

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors. Specific changes to the originally proposed labeling have been identified in this review.

B. Recommendation on Phase 4 Studies and Risk Management Steps

Additional adequate and well-controlled studies are recommended to better quantitative the effect of tadalafil on color vision and retinal physiology (as measured by ERG testing). In particular, testing after repeated dosing should be performed.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two clinical studies evaluating vision were performed with tadalafil. Each study is so flawed by its execution and analysis that it is not possible to quantitate the effect of tadalafil on vision.

Flaws in Protocol H6D-EW-LVAN include:

- Failure to record to position of the errors in the Farnsworth-Munsell test.
- Inconsistent visual acuity scores even without treatment (may reflect inconsistent refractive correction).
- Ocular motility and cover tests changing even without treatment
- Visual acuity scores which are not physiologic.
- Failure to perform scheduled ERG testing on 4 of 18 patients at hour 7
- Failure to perform scheduled ERG testing in most patients at hour 26.

Flaws in Protocol H6D-EW-LVCN include:

- Failure to analyze the results of the Farnsworth-Munsell test according to the protocol plan.
- Failure to show that the positive control had positive findings.
- Reporting of test results as normal or abnormal when the test result is a numerical value and failing to include the value of the test result.

B. Efficacy

Not evaluated in this review.

C. Safety

Minimal information is available from these studies; however, abnormal color vision was reported. No significant differences in comparison to sildenafil can be determined.

Vision Studies

Title: A Double-blind, Randomized, Placebo-controlled, Three-Period, Cross-over Study to Explore the Effects of IC351 (LY450190) in Single Oral Doses on Visual Function in Healthy Male Subjects (Protocol H6D-EW-LVAN)

Investigator: _____

Study Centre: _____

Dates of Study: 24 March 2000 through 17 May 2000.

Clinical Phase: Phase 1

Objectives

- To assess the effect of IC351 in single oral doses on colour vision, in healthy subjects.
- To explore the effect of IC351 on visual functions (electroretinogram, intra-ocular pressure, visual field),
- To assess the safety and tolerability of IC351,
- To document the time course of IC351 in plasma.

Study Design

Single center, double-blind, randomized, placebo-controlled, 3-period cross-over study to be performed on 18 healthy male subjects (18-45 years of age). The subjects were observed over 3 periods. To maintain the double-blind nature of the study, IC351 and/or placebo tablets were administered in combination so that each subject received the same number of tablets in each treatment period. Each subject received a total of two tablets of a combination of IC351 and/or placebo (2 x 10 mg IC351 tablets for the 20 mg dose, 1 x 10 mg IC351 and 1 x placebo for the 10 mg dose, and 2 x placebo tablets for the placebo treatment). After an overnight fast, in each treatment period, IC351 and/or placebo tablets were administered orally with a total of 200 mL of water at room temperature. Tablets were administered to each subject whilst the subject was standing in an upright position. Subjects were not allowed to lie supine for 2 hours. The 10 mg IC351 market image and placebo tablets were prepared by Lilly ICOS LLC and supplied in bottles.

Reviewer's Comments: *18 patients may be enough to detect a change, but 18 patients are not enough to rule out an effect on vision. This comment was previously provided at the time the study was proposed.*

Study Plan					
			Treatment Periods 1, 2 and 3		
Assessment	Screening	Day -1	Days 1 and 2		Poststudy
Informed consent	X	X[a]			
Inclusion/exclusion criteria	X				
Demographic data	X				
Medical history	X				
Urinary drug screen	X	X			
Serology	X[b]				
Study drug administration:			Day 1 (0 h)		
Safety and tolerability:					
Adverse event questioning	X		Adverse events were monitored continuously during the study		
Vital signs	X				X
12-lead ECG	X		Predose, 3 and 24 hours postdose		X
Clinical laboratory evaluations	X				X
Physical examination	X				X
Visual function tests:					
Ishihara test	X				
FM 100-hue test	X	X	2, 6 and 24 hours postdose		
Visual field, sight and visual coordination, examination of Anterior and posterior eye Segments, intra-ocular pressure		X	3 and approximately 25 hours postdose (starting times)		
Electroretinogram		X[c]	Approximately 7 to 8 hours postdose and approximately 26 hours postdose		
Pharmacokinetics:					
Blood sampling			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours postdose		

[a] Informed consent signed on admission to Treatment Period 1 only

[b] Hepatitis and HIV tests

[c] Period 1 only

Pharmacodynamic Methods

An Ishihara plates test for colour vision was performed at screening only.

The following tests of visual function were performed at specific times during the study. Where these tests were performed at similar times, they were performed in the order shown below:

FM (Farnsworth-Munsell) 100-hue test for colour vision. The total number of errors will be tabulated as well as a graphical representation of errors (position and significance). The test will be carried out for each eye separately

Centre-30 degree visual field assessment.

Distant vision (Snellen test), near vision (according to Keeler) and visual co-ordination (cover test, ocular motility and pupil reaction).

Examination of anterior segments (slit lamp of —) and posterior segments (lens of —) of the eye.

Measurement of intra-ocular pressure was performed using a ——————— under local anaesthesia with oxybuprocaine.

A Flash Ganzfeld full-field electroretinogram (ERG) was performed in the presence of mydriatic eye drops (0.5% tropicamide) under local anaesthesia with oxybuprocaine. The ERG was performed after completing all other visual tests and in accordance with the recommendations of the International Society for Clinical Electrophysiology of Vision (Marmor and Zrenner 1995).

Additional tests may have been performed where clinically indicated, although these were not to have interfered with the primary assessment of colour vision (FM 100-hue test).

Clinical interpretation of the visual function data, where appropriate, was provided by the same Ophthalmology Consultant throughout the study.

Reviewer Comments: *As noted above, the FM was to have a graphical representation of error (position and significance). This is a standard clinical report of this test but was not carried out in this study.*

Changes in the Conduct of the Study or Planned Analyses

Except for Subjects 1 and 4 in Treatment Period 1, the ERG at 26 hours postdose in all treatment periods could not be performed due to corneal and/or conjunctival punctate staining, which was related to the contact lenses used in the ERG procedure. The ophthalmology consultant recommended that the ERG should not be performed at this time point in all treatment periods, due to the risk of corneal staining and contact lens complications. As a result, there were insufficient ERG data to perform a repeated measures analysis. Alternatively, the 7 hour ERG data were analyzed using a mixed effects model. The average of both eyes was used as the response variable for statistical analysis of the ERG data; however additional analyses were also performed separately for the left and right eyes, due to the ERG being performed at a single time point for one eye only for some subjects.

The data for the primary FM 100-hue test were not transformed using natural logs prior to analysis due to the occurrence of zero values. Due to the evidence of non-normality in the relationship between the mean and variance and the evidence of a period effect, the FM 100-hue error scores were analyzed using the method outlined by (Senn 1993). It was not possible to represent results obtained from these analyses graphically and the variance components for the inter-subject (between) and intra-subject (within) variability for the main pharmacodynamic parameters could not be obtained using the mixed-effects linear model. The validity of presenting non-parametric confidence intervals based on the Wilcoxon signed rank test (Gardner and Altman 1993) was investigated as a means of presenting confidence intervals. This method does not take period effects into account and was found to be unsuitable because of the strong period effects evident in this study.

The protocol stated that only the data measured at 2 hours postdose for the secondary endpoints would be analyzed untransformed. As the secondary endpoints were not measured at 2 hours, all data for the secondary endpoints were analyzed untransformed.

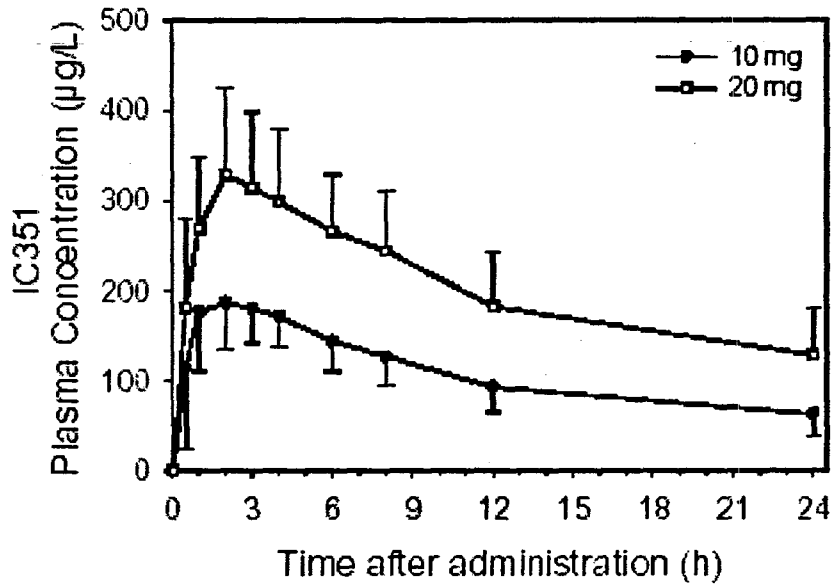
Geometric standard deviation was not presented for the pharmacokinetic parameters, as this was not considered to be an appropriate summary statistic.

Reviewer Comments: *These changes are considered significant deviations from the planned study.*

Demographic Data							
Subject number	Gender	Age (years)	Body weight (kg)	Height (cm)	BMI (kg/m^2)	Smoking status (cigarettes/day or grams tobacco/week)	Alcohol consumption (units/week)[a]
1	Male	30	71.8	172	24.3	0	1
2	Male	27	59.6	174	19.7	0	0
3	Male	25	77.7	185	22.7	0	2
4	Male	21	81.5	179	25.4	7 cigarettes	2
5	Male	22	77.8	186	22.5	0	7
6	Male	22	96.6	186	27.9	0	26
7	Male	19	73.3	186	21.2	0	4
8	Male	25	74.2	179	23.2	5 cigarettes	0
9	Male	24	65.1	167	23.3	9 cigarettes	12
10	Male	33	77.8	178	24.6	1 cigarette	14
11	Male	28	76.2	186	22.0	0	10
12	Male	27	66.0	178	20.8	0	1
13	Male	21	80.7	173	27.0	0	18
14	Male	33	76.0	177	24.3	0	24
15	Male	22	92.6	188	26.2	0	10
16	Male	27	60.7	172	20.5	0	10
17	Male	25	84.7	181	25.9	0	10
18	Male	26	77.2	184	22.8	0	20
Mean (SD)		25	76.1	180	23.6		
		(4.0)	(9.67)	(6.2)	(2.31)		

[a] One unit of alcohol equals 8 g ethanol (¼ litre of beer or lager, one glass (ca. 125 mL) of wine or one measure (ca. 25 mL) of spirits)

Plasma Concentrations



µg/L is equivalent to ng/mL.

Figure LVAN.11.1. **Arithmetic Mean (SD) Plasma Concentration-Time Profiles of IC351 Following Oral Administration of Single 10 and 20 mg Doses (N=18).**

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Visual Acuity – selected patients with inconsistent findings listed below

Subject number: 2		Age: 27 years			Body weight: 59.6 kg				
Treatment sequence: CAB									
		Screening		Admission		3 h		25 h	
Treatment	Test	Left	Right	Left	Right	Left	Right	Left	Right
C	Distance	6	6	9	12	9	9	9	9
	Near vision	8	8	5	6	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
A	Distance			9	12	9	9	9	9
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
B	Distance			9	9	9	9	9	9
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
Subject number: 3		Age: 25 years			Body weight: 77.7 kg				
Treatment sequence: CBA									
		Screening		Admission		3 h		25 h	
Treatment	Test	Left	Right	Left	Right	Left	Right	Left	Right
C	Distance	6	9	9	9	6	12	6	12
	Near vision	5	5	5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
B	Distance			9	24	9	12	9	12
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
A	Distance			6	12	9	12	6	12
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
Subject number: 6		Age: 22 years			Body weight: 96.6 kg				
Treatment sequence: CAB									
		Screening		Admission		3 h		25 h	
Treatment	Test	Left	Right	Left	Right	Left	Right	Left	Right
C	Distance	9	6	18	9	12	9	9	12
	Near vision	8	5	5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Abnormal	Abnormal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
A	Distance			2	6	12	9	12	12
	Near vision			8	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal
B	Distance			9	5	9	6	9	9
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal

Visual Acuity – selected patients with inconsistent findings listed below (continued)

Subject number: 8		Age: 25 years		Body weight: 74.2 kg					
Treatment sequence: BCA									
		Screening		Admission		3 h		25 h	
Treatment	Test	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
B	Distance	4	4	6	6	9	6	9	6
	Near vision	5	5	5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
C	Distance			9	9	9	6	9	6
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Abnormal	Abnormal	Normal	Normal	Normal	Normal
A	Distance			9	6	9	6	9	6
	Near vision			5	5	5	5	5	5
	Pupil reaction			Normal	Normal	Normal	Normal	Normal	Normal
	Ocular motility			Normal	Normal	Normal	Normal	Normal	Normal
	Cover test			Normal	Normal	Normal	Normal	Normal	Normal

Reviewer Comments: *There are multiple problems with the values listed in this report. Patients are reported to have abnormal findings at admission into the trial, which are corrected after administration of test drug or placebo. Visual acuities are inconsistently worse at admission or with placebo. Some recorded visual acuities are not physiologically possible (Patient 6 on admission with sequence A). If the acuities are accurate, then patients were not properly corrected with glasses before testing, and the results of the testing are inaccurate.*

APPEARS THIS WAY
ON ORIGINAL

Color Vision

	Summary of colour vision test (FM 100-hue) error scores								
		Left eye				Right eye			
Treatment		Admission	2 h	6 h	24 h	Admission	2 h	6 h	24 h
10 mg IC351	Arithmetic mean	15	14	11	10	12	12	16	10
	Arithmetic SD	14.9	13.5	6.2	7.0	13.2	10.0	14.5	9.0
	Median	10	8	8	8	8	8	12	8
	Min								
	Max								
	N	18	18	18	18	18	18	18	18
20 mg IC351	Arithmetic mean	9	8	10	10	12	16	14	12
	Arithmetic SD	6.8	9.3	10.6	11.9	15.4	12.5	13.2	10.3
	Median	8	4	8	8	6	14	10	8
	Min								
	Max								
	N	18	18	18	18	18	18	18	18
Placebo	Arithmetic mean	14	12	10	8	14	12	15	11
	Arithmetic SD	10.7	9.0	9.0	8.3	13.8	9.7	14.2	13.8
	Median	12	10	10	4	12	8	8	6
	Min								
	Max								
	N	18	18	18	18	18	18	18	18

Reviewer Comments: *The results of the FM-100 hue do not appear to have been recorded correctly. Total error score is just one part of the testing result. Equally important is whether the confusion is spread throughout the color spectrum or focused in a particular pattern. The particular pattern does not appear to have been collected.*

APPEARS THIS WAY ON ORIGINAL

Visual Field

	Summary of visual fields deficit (dB)						
		Left eye			Right eye		
Treatment		Admission	3 h	25 h	Admission	3 h	25 h
10 mg IC351	Arithmetic mean	0.07	0.23	0.12	0.07	0.07	0.00
	Arithmetic SD	0.221	0.492	0.514	0.347	0.269	0.329
	Median	-0.01	0.14	-0.02	-0.03	0.08	-0.07
	Min						
	Max						
	N	18	18	18	18	18	18
20 mg IC351	Arithmetic mean	0.16	0.08	0.18	0.18	0.09	-0.02
	Arithmetic SD	0.337	0.188	0.322	0.321	0.251	0.193
	Median	0.04	0.06	0.07	0.16	0.04	-0.05
	Min						
	Max						
	N	18	17	18	18	18	18
Placebo	Arithmetic mean	0.17	0.33	0.11	0.20	0.18	0.05
	Arithmetic SD	0.313	0.660	0.390	0.400	0.351	0.322
	Median	0.03	0.02	0.02	0.11	0.09	-0.03
	Min						
	Max						
	N	18	18	18	18	18	18

Reviewer Comments: *The results of the visual field testing cannot be reliably interpreted due to the inconsistent findings in the visual acuity. No significant differences were observed between groups. However, the variability was high.*

APPEARS THIS WAY
ON ORIGINAL

ERG

Statistical Comparison of Amplitude and Implicit Time (Average of Both Eyes) for Photopic ERGs at 7 Hours After Oral Administration of Single Doses of 10 and 20 mg IC351 and Placebo

		Difference between LS means (95% CI)	
Parameter		10 mg IC351-placebo	20 mg IC351-placebo
Amplitude	White light a1	-6.4 (-19.3, 6.4)	-6.8 (-19.9, 6.3)
(μV)	White light b1	21.2 (2.2, 40.1)	22.6 (3.2, 41.9)
	Red light a1	-1.8 (-5.2, 1.6)	-0.2 (-3.6, 3.2)
	Red light b1	2.0 (-6.2, 10.2)	-1.1 (-9.4, 7.1)
	Blue light a1	-1.4 (-6.2, 3.4)	0.2 (-4.7, 5.1)
	Blue light b1	11.7 (-6.6, 30.0)	10.5 (-8.1, 29.2)
Implicit time	White light a1	-0.3 (-1.0, 0.5)	0.5 (-0.3, 1.2)
(ms)	White light b1	-0.4 (-2.7, 1.9)	1.1 (-1.2, 3.5)
	Red light a1	0.2 (-0.5, 1.0)	0.2 (-0.6, 0.9)
	Red light b1	0.5 (-1.0, 1.9)	0.3 (-1.1, 1.7)
	Blue light a1	0.0 (-0.6, 0.7)	0.0 (-0.7, 0.7)
	Blue light b1	0.3 (-2.3, 3.0)	1.3 (-1.4, 4.0)

Mean amplitudes for white light b1 and blue light b1 were higher for active doses than for placebo. These differences were relatively small and displayed large variability. Mean amplitudes and implicit times were similar between the 10 and 20 mg dose levels of IC351. The results for the left and right eyes separately were similar to those noted above. The planned ERGs at 26 hours postdose were not performed for most subjects, due to corneal and/or conjunctival punctate staining which was related to the contact lenses used in the ERG procedure.

Reviewer Comments: *The results from the ERG cannot be reliably interpreted. Four of the eighteen patients (#5, 13, 17 and 18) did not complete one or more of their scheduled ERGs (in addition to the failure to collect ERGs at hour 26). Patient 11, when receiving 10mg IC351, had a reduced amplitude to red light. Patient 7, when receiving placebo, had a reduced amplitude to red light.*

IOP

		Summary of intraocular pressure (mmHg)					
		Left eye			Right eye		
Treatment		Admission	3 h	25 h	Admission	3 h	25 h
10 mg IC351	Arithmetic mean	12	13	13	12	13	12
	Arithmetic SD	2.5	2.8	1.8	2.8	3.0	2.6
	Median	12	13	13	12	12	12
	Min						
	Max						
	N	18	18	17	18	18	18
20 mg IC351	Arithmetic mean	12	13	13	12	13	13
	Arithmetic SD	2.2	2.9	2.5	2.9	3.1	2.4
	Median	12	14	12	12	14	13
	Min						
	Max						
	N	18	18	18	18	18	18
Placebo	Arithmetic mean	13	12	12	13	12	11
	Arithmetic SD	2.0	1.6	2.0	2.1	2.3	2.3
	Median	13	12	12	13	12	10
	Min						
	Max						
	N	18	18	16	18	18	16

Reviewer Comments: *No significant changes in IOP have been noted.*

Frequency of Drug-Related Treatment-Emergent Adverse [number of subjects with event]			
	10 mg IC351	20 mg IC351	Placebo
COSTART preferred term	(N=18)	(N=18)	(N=18)
Headache	3 [3]	3 [3]	1 [1]
Myalgia	1 [1]	3 [3]	0
Thinking abnormal	0	1 [1]	0
Visual field deficit	0	0	1 [1]
Total	**4 [4]**	**7 [6]**	**2 [2]**

Reviewer Comments: *No significant visual events were reported as adverse experiences; however the number of subjects in the study is small.*

Study Summary

The study is sufficiently flawed in its execution and analysis so as to prohibit any conclusions with respect to ocular findings.

Title: A Study to Investigate the Effects of IC351 and Sildenafil on Colour Vision in Healthy Subjects

Investigator: [redacted]

Study Centre: [redacted]

Dates of Study: 17 March 2000 through 05 July 2000.

Clinical Phase: Phase 1.

Protoco: IC351 H6D-EW-LVCN Main Report

Study Objectives

- To assess the proportion of healthy subjects reporting visual function abnormalities (blue vision) after the administration of a 100 mg dose of sildenafil and after a 20 mg dose of IC351, as determined by the Farnsworth-Munsell (FM-100) test.
- To assess whether subjects who have in the past reported blue vision whilst taking sildenafil report blue vision after taking IC351.
- To further assess the safety and tolerability of single oral doses of IC351.

Overall Study Design and Plan: Description

This was an Investigator and subject-blind, randomized, two-period, two-treatment crossover study to investigate the effects of IC351 and sildenafil on colour vision in 60 healthy male subjects. It was planned to study an additional sub-group of approximately six subjects who had previously reported blue vision after sildenafil administration. This proved unsuccessful, however, as the Investigator was unable to recruit these subjects.

Screening was performed in the 14 day period prior to the first admission. In the first treatment period, subjects received either a single oral dose of 20 mg IC351 or a single oral dose of 100 mg sildenafil. In the second treatment period, subjects received the alternative treatment to that administered in the first treatment period. In each treatment period, dosing occurred on Day 1. Thereafter, subjects remained in the Unit until Day 2, approximately 24 hours after dosing. There was an interval of at least 10 days between dosing in each treatment period.

Study Population

Inclusion Criteria

Subjects were included in the study if they met all of the following criteria:

- Healthy male subjects as determined by medical history and physical examination,
- Between the ages of 18 and 65 years, inclusive
- BodyMass Index (BMI) between 19 and 29 kg/m^2, inclusive,
- Subjects who were reliable and willing to make themselves available for the duration of the study, and who would abide by the study restrictions,
- For the sub-population only, subjects who had previously experienced blue vision whilst taking sildenafil.

Exclusion Criteria

Subjects were excluded from the study for any of the following reasons:

- Any clinically significant abnormality of the visual tests or significant ophthalmologic disease
- Any clinically significant abnormality of any of the haematology, clinical chemistry or urinary tests
- Positive human immunodeficiency virus (HIV) antibody test, positive hepatitis B and/or C serology
- Any clinically significant abnormality of the 12-lead ECG, particularly those which were considered related to ischaemia
- Subjects who were unable to correctly order the cubes in the FM-100 Hue colour vision discrimination test at screening, in the opinion of the ophthalmologist.
- Particular attention was made to the ordering of the blue cubes
- Subjects with angina or heart failure who were potential recipients or users of nitrates
- Previous users of sildenafil (except the sub-group who had previously reported blue vision)
- Any medically significant history of neurological disease, cancer, or cardiac (especially conduction disturbance), metabolic, hepatic, renal, gastrointestinal (except appendectomy), venereal, haematological disorder or disease
- History of alcoholism and/or substance abuse; positive findings on either urinary drug screening or ethanol test
- Subjects who had an alcoholic intake greater than 28 units* per week, or subjects unwilling to stop alcohol consumption for the duration of the study * 1 unit = 8 g ethanol (1/4 litre beer, 0.1 L of wine or 1 measure of spirits)
- History of severe allergies or multiple adverse drug reactions
- Known allergies or significant hypersensitivity to IC351, sildenafil or related drugs
- Known allergies to tropicamide and/or oxybuprocaine
- History of excessive xanthine use within the 6 months preceding the study
- Any subject who had received prescribed medication with known effects on cytochrome P450 3A4 within 14 days of the first study day, or non-prescribed over-the-counter (OTC) medication within 7 days of the first study drug administration, or any medication that would need to be continued during the study, apart from vitamin/mineral supplements and occasional paracetamol or ibuprofen
- Any subject who had received a new chemical entity (NCE) within 3 months or an investigational medication within 1 month prior to the start of this study, or who was scheduled to receive an investigational drug other than IC351 during the course of this study
- Blood donation of greater than 500 mL in the 3 months preceding the study
- Previously admitted to the study
- Subjects who were unable to perform the FM 100-hue test without glasses or contact lenses
- Any other conditions which in the opinion of the Investigator precluded participation in the study.

Treatments Administered

In each treatment period, subjects received two capsules, each capsule either containing a tablet of IC351 (10 mg, market image) or containing two tablets (2 x 25 mg) of sildenafil. In each treatment period, the capsules containing IC351 or sildenafil were administered orally with a total of 200 mL of water for each subject. Subjects received the dose of IC351 or sildenafil whilst in an upright standing position. Following dosing, subjects were not allowed to lie supine for 2 hours postdose, except for study procedures or where clinically indicated.

Blinding

In order to maintain the Investigator and subject-blind nature of the study, capsules were not identified as IC351 or sildenafil. Sildenafil capsules were identical in appearance to those for IC351.

Study Plan				
			Treatment Periods 1 and 2	
Assessment	Screening	Day -1	Days 1 and 2	Poststudy
Informed consent	X	X[a]		
Inclusion/exclusion criteria	X			
Demographic data	X			
Medical history	X			
Urinary drug screen[b]	X	X		
Alcohol breath test	X	X		X
Serology	X			
Study drug administration:			IC351 or sildenafil at 0 h (Day 1)	
Safety and tolerability:				
Adverse event questioning			Predose and 2 and 24 h postdose	X
Body weight	X	X		X
Vital signs	X	X	Predose, 2 and 24 h postdose	X
12-lead ECG	X	X	Predose and 2 and 24 h postdose	X
Clinical laboratory evaluations	X	X		X
Physical examination	X			X
Visual field test	X			
Sight assessments, distance, near vision, co-ordination and refraction	X			X
Anterior and posterior segments	X	X	2 and 24 h postdose	X
Intraocular pressure	X	X	2 and 24 h postdose	X
Farnsworth Munsell 100–hue test	X	X[c]	1, 2 and 24 h postdose	X
Electroretinogram	X	X	2 h postdose	X
[a] Informed consent signed on admission to Treatment Period 1 only				
[b] Full urinary drug screen performed at screening only; limited screen for drugs of abuse and alcohol only performed at other times indicated				
[c] Test performed on two occasions				

The following visual tests were performed at specific times during the study for each eye separately:

- Visual field test (Humphrey analyser)
- Sight assessments: distance (Snellen test), near vision (according to Nieden), co-ordination (Worth and Schober test) and refraction (Humphrey test with dioptron)
- The FM 100-hue colour vision test
- The Flash Ganzfeld full-field ERG in the presence of mydriatic eye drops (tropicamide) and local anaesthetic (oxybuprocaine) was assessed for white and blue light. The ERG was recorded according to the recommendation of the International Society for Clinical Electrophysiology of Vision (Marmor and Zrenner 1995)
- Other visual tests (sight examination of the anterior and posterior segments (slit lamp of ————), measurements of intraocular pressure (according to Goldmann, anaesthesia with eye drops containing oxybuprocaine)

The following tests were performed in sequence during each treatment period:
- FM 100-hue colour vision test
- Examination of the anterior and posterior segments and measurement of intraocular pressure (could be performed simultaneously)
- Flash Ganzfeld full-field ERG

If one of the above mentioned tests was abnormal, additional tests could be performed at the discretion of the Investigator but without interfering with the colour vision test.

Determination of Sample Size
The assumed probability of observing blue vision following sildenafil administration was approximately 10% (Center for Drug Evaluation and Research, 1998, Viagra® package insert, Goldstein *et al.* 1998). With 60 subjects completing the study, the probability of six or more subjects taking sildenafil experiencing blue vision was 66%.

For a sample size of 60, if no blue vision was experienced by subjects taking IC351, the upper limit of the 95% CI for the probability of blue vision on IC351 was 4.9%.

Changes in the Conduct of the Study or Planned Analyses
The trial was initially intended to study a sub-group of six subjects who had previously reported blue vision after sildenafil administration. This was not performed, however, as the Investigator was unable to recruit these subjects.

The total number of errors in the FM 100-hue colour vision test were not recorded as described in the protocol. Instead, the following rules were applied when interpreting the results:

A deviation of up to 3 steps in the sequence of the numbers was considered normal, and the deviation was not documented.

Deviations of between 3 and 5 steps in the sequence of numbers were considered borderline and recorded.

Deviations of more than 5 steps in the sequence of numbers were considered pathologic or clinically significant only when they were always in the same place of the colour scale, thus indicating defective colour vision.

Isolated deviations of more than 5 steps in the sequence of numbers in different places of the colour scale were defined as 'careless mistakes' and were not recorded as being clinically significant.

The normal approximation to the binomial distribution was not utilized as planned as the number of occurrences of blue vision were too few for the approximation to be valid. Exact confidence intervals were calculated using the F-distribution link to the binomial distribution method.

Reviewer Comments: *This change in analysis is not consistent with the standard method of analysis.*

Study Subjects

Sixty subjects entered and completed the study. A sub-group of six subjects who had previously reported blue vision after sildenafil administration was not studied as the Investigator was unable to recruit these subjects.

All available pharmacodynamic data for all subjects who entered the study are presented in the individual data listings and are included in the summary statistics.

There were no abnormalities detected in the sight assessments conducted at screening (distance (Snellen test), near vision (according to Nieden) and co-ordination (Worth and Schober test and refraction (Humphrey test with dioptron)) for any subject. In addition, there were no clinically significant abnormalities in the external tests for sight (sight examination of the anterior and posterior segments (slit lamp of l ——— during the study for both treatments.

Reviewer Comments: *Actual values for the test results have not been provided. Tests such as refraction have values listed as "normal." Refractions are not normal versus abnormal, but instead should have a particular value associated with them. The results cannot be verified.*

Summary of the colour vision test (FM 100-hue)											
			Left eye					Right eye			
Treatment		Admin 1	Admin 2	1 h	2 h	24 h	Admin 1	Admin 2	1 h	2 h	24 h
	N	60	60	60	60	60	60	60	60	60	60
20 mg	Proportion (%)of subjects with normal colour vision	100	100	100	100	100	100	100	100	100	100
100 mg	Proportion (%)of subjects with normal colour vision	100	100	100	100	100	100	100	100	100	100

A total of 44 of the 60 subjects studied exhibited deviations of up to 10 steps in the sequence of numbered blocks in the FM 100-hue colour vision test at some time during the study. Deviations of more than 5 steps in the sequence of numbers were considered pathologic or clinically significant only when they were always in the same place of the colour scale, thus indicating defective colour vision. All deviations recorded during the study were considered to be normal, borderline or careless mistakes and none were considered clinically significant.

Reviewer Comments: *The basis for claiming that these deviations are normal is not clinically supported. Approximately one third of all patients had a 4, 5, or 6 step error in the FM-100 test at one or two hours after dosing of IC351 and approximately one third of all patients had a 4, 5, or 6 step error in the FM-100 test at one or two hours after dosing sildenafil. In the absence of a negative control group, this is suggestive of a similar effect between IC351 and sildenafil with respect to changes in color vision. Sildenafil is known to have an effect on color vision. The actual plotted exam results have not been presented.*

Statistical analysis of reports of blue vision recorded as adverse events						
		95% confidence limits		95% confidence limits		
	100 mg Sildenafil	Lower	Upper	20 mg IC351	Lower	Upper
Proportion (%) of healthy subjects reporting blue vision#	3.3	0.4	11.5	1.7	0.0	8.9
60 Total number of subjects evaluated for pharmacodynamics						
# as reported by subject as an adverse event						

Subjects 3 and 9 (following 100 mg sildenafil) and Subject 48 (following 20 mg IC351) experienced adverse events of blue vision during the study. These reports of chromatopsia did not coincide with errors in the FM 100-hue colour vision test for any subject with the exception of Subject 48. At 1 h postdose (30 minutes after the onset of blue vision), Subject 48 placed blocks of the test out of sequence by 4, 5, 5 and 4 steps. None of these deviations were considered to be clinically significant. In addition, this subject made similar errors of 4 and 5 steps at admission to both treatment periods and of 4 steps at 24 hours after sildenafil administration which did not coincide with the adverse event of chromatopsia.

Reviewer Comments: *Disagree with the conclusion that these deviations in the FM 100-hue color vision test are not clinically significant.*

Statistical analysis showed that the percentage of subjects that experienced blue vision (reported as an adverse event) following administration of sildenafil was significant (3.3% with an associated 95% CI of 0.4 to 11.5%) as the CI excluded zero. In contrast, the percentage of subjects that experienced blue vision following administration of IC351 was 1.7% with an associated 95%CI of 0 to 8.9%.

Reviewer Comments: *The difference in reporting of blue vision between sildenafil and IC351 was not statistically significant. The rate of blue vision with IC351 by this report may be as high as 8.9%.*

A previous study designed to investigate the effects of a single oral dose of sildenafil (200 mg) on visual function concluded that aberrations in colour vision were detectable by amplitude reduction and delays in the ERG waveform, although effects were small compared with both intra and inter-subject variability (Center for Drug Evaluation and Research, NDA-20-895). During the present study, ERG data were collected at admission and 2 h postdose, the latter timepoint coinciding with the blue vision reported by Subjects 3 and 9 (following 100 mg sildenafil) and Subject 48 (following 20 mg IC351). Examination of the ERG data collected at 2 h postdose for these subjects showed them to be comparable to predose data in both amplitude and latency. Furthermore, all ERG examinations were considered normal by the Ophthalmologist.

Reviewer Comments: *The actual values of the ERG data have not been provided. Potential changes in amplitude and latency cannot be verified.*

Intraocular pressure measurements remained similar throughout the study with mean values of 17 to 18 mmHg recorded for both treatments (reference range 15 to 22 mmHg). Individual intraocular pressure measurements were 15 to 21 and 15 to 20 mmHg following IC351 and sildenafil, respectively.

Reviewer Comments: *Agree.*

Summary of Adverse Events

The overall incidence of treatment-emergent adverse events is summarized below:

Frequency of treatment-emergent adverse events (all causalities)			
		Number of adverse events [Number of subjects with adverse event]	
		20 mg IC351	100 mg Sildenafil
COSTART Body system	COSTART term	(N=60)	(N=60)
Body as a whole	Headache	18 [12]	11 [9]
	Back pain	15 [11]	4 [4]
	Asthenia	3 [3]	2 [2]
	Face edema	1 [1]	
	Pain	1 [1]	
Musculo skeletal system	Myalgia	9 [9]	7 [5]
	Arthralgia	2 [2]	
Digestive system	Dyspepsia	4 [2]	2 [1]
	Diarrhea		2 [2]
	Nausea	1 [1]	1 [1]
	Increased appetite		1 [1]
Special senses	Chromatopsia	1 [1]	2 [2]
	Amblyopia		1 [1]
Nervous system	Paresthesia	1 [1]	1 [1]
	Dizziness	1 [1]	
Respiratory system	Rhinitis	1 [1]	1 [1]
	Pharyngitis	1 [1]	

8 page(s) of revised draft labeling has been redacted from this portion of the review.

Regulatory Recommendation:

It is recommended that the labeling be revised as identified in this review.

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

cc: NDA 21-368
HFD-580
HFD-105
HFD-550/Consult File
HFD-580/PM/Spell Lesane
HFD-580/MO/Hirsch
HFD-550/Chambers