Event Classification	n (%)	n (%)
HEADACHE	3 (6.4)	34 (36.6)
DYSPEPSIA	0	17 (18.3)
BACK PAIN	6 (12.8)	10 (10.8)
MYALGIA	1 (2.1)	8 (8.6)
PHARYNGITIS	0	8 (8.6)
SURGICAL PROCEDURE	6 (12.8)	8 (8.6)
DIARRHEA	2 (4.3)	7 (7.5)
UNEXPECTED BENEFIT	1 (2.1)	7 (7.5)
ARTHRALGIA	2 (4.3)	6 (6.5)
ACCIDENTAL INJURY	6 (12.8)	5 (5.4)
COUGH INCREASED	2 (4.3)	5 (5.4)
NAUSEA	0	5 (5.4)
VASODILATATION	0	5 (5.4)
ABDOMINAL PAIN	1 (2.1)	4 (4.3)
GOUT	0	4 (4.3)

Treatment-emergent adverse events noted in more than 5% of patients treated with 20 mg IC351 included back pain (10.8% IC351 treatment group, 12.8% placebo group), myalgia (8.6% IC351 treatment group, 2.1% placebo group), pharyngitis (8.6% IC351 treatment group, 0% placebo group), surgical procedure (8.6% IC351 treatment group, 12.8% placebo group), diarrhea (7.5% IC351 treatment group, 4.3% placebo group), unexpected benefit (7.5% IC351 treatment group, 2.1% placebo group), arthralgia (6.5% IC351 treatment group, 4.3% placebo group), accidental injury (5.4% IC351 treatment group, 12.8% placebo group), cough increased (5.4% IC351 treatment group, 4.3% placebo group), nausea (5.4% IC351 treatment group, 0% placebo group), and vasodilatation (5.4% IC351 treatment group, 0% placebo group).

Medical Officers Comments:

The common adverse events , headache , dyspepsia, back pain and myalgia occurred at a higher rate than seen in other pivotal studies.

Potential cardiovascular-related treatment-emergent adverse events occurred at a low incidence. Vasodilatation occurred in five patients (5.4%) in the IC351 treatment group and no patient in the placebo group. Dizziness occurred in two patients (4.3%) in the placebo group and in one patient (1.1%) in the IC351 treatment group. Syncope was reported in two patients treated with placebo and in no patient treated with 20 mg IC351. A single patient treated with 20 mg IC351 reported palpitations (a transient increase in heart rate) without other symptoms. One patient treated with 20 mg IC351 reported arrhythmia which was found to be sinus arrhythmia.

Medical officers Comments:

The treatment emergent adverse events were unusually high in this australian study. More than 1/3 of the treated patients had headache. The incidence of treatment related common AE's was also much higher than the other studies.

Deaths
No deaths occurred in this study.

Serious Adverse Events

There were 5 patients who experienced serious adverse events in this study. None of the serious adverse events, in the opinion of the investigator, was judged likely to have been related to the study drug or protocol procedures. All five cases met the criteria for seriousness: all events resulted in hospitalization. Of the 5 patients who experienced a serious adverse event, 3 were taking placebo (perianal abcess, umbilical hernia with wound infection, and central cord injury following bicycle accident) and 2 were being treated with 20 mg IC351 (nasal polypectomy, and gouty arthritis of the left knee).

Medical officers Comments:
The reviewer agrees with the sponsor's assessment of SAE's

Non serious Clinically Significant Adverse Events

Seven patients experienced a non serious clinically significant adverse event during this study. A total of 4 patients, all in the IC351 treatment group, discontinued due to adverse events.

Patient 502-5116, who received treatment with 20 mg IC351, noted headaches after his first two doses of study medication. The headaches were relieved by acetaminophen and there were no other neurological symptoms. The investigator reported the event as possibly related to study medication. At Visit 3, without taking another dose of the study medication, the patient discontinued from the study.

Patient 500-5005, who received treatment with 20 mg IC351, noted a headache after his first and only dose of study medication. The headache was reported 1.5 hours after taking IC351. The patient took no analgesics and the headache resolved spontaneously within 2 hours. At Visit 3, without taking another dose of the study medication, the patient discontinued from the study.

Patient 502-5115, who received treatment with 20 mg IC351, experienced intermittent dyspepsia while participating in the study. The patient had a preexisting history of reflux esophagitis with onset in 1996. At Visit 5, the patient discontinued from the study due to dyspepsia.

Patient 504-5252, who received treatment with 20 mg IC351, reported the onset of dyspepsia before receiving his first dose of study drug. At Visit 3, after taking five doses of study drug, the patient discontinued from the study.

Patient 502-5103, who received treatment with 20 mg IC351, developed an urticarial rash with accompanying face and tongue edema after having dinner at a local restaurant. The patient fully recovered and continued taking IC351 with no recurrent urticaria or face/tongue edema. The investigator stated the event was likely due to patient ingesting an allergenic food substance.

Patient 504–5243 who received treatment with 20 mg IC351 was discovered to have an esophageal stricture and esophageal ulceration. The patient had a preexisting history of esophageal reflux with onset in 1996. Endoscopic evaluation revealed an esophageal stricture and ulceration. Biopsy was benign, the stricture was dilated and the patient's symptoms were improved with omeprazole 20 mg. The investigator ascribed the patient's symptoms to his preexisting esophageal reflux. The patient continued in the study on IC351 without incident.

Patient 504-5238, who received treatment with placebo, experienced a transient vasovagal reaction several hours after moderate physical exertion on a humid day. A CT scan of the head was negative. The patient continued in the study with no additional syncopal episodes. The investigator did not believe the event was related to study drug or procedures.

Clinical Laboratory Evaluation

Criteria for clinically significant laboratory values in this study were not established a priori. The central laboratory defined the normal range for each laboratory parameter. Each investigator determined clinically relevant laboratory values.

Individual Patient Changes and Clinically Significant Abnormalities

Patient 501-5056, who received treatment with 20 mg IC351, demonstrated transient elevations in liver function tests during the study. The patient had a mildly elevated ALT atscreening Visit1 of66 U/Land atVisit2 of 53 U/L(normalrange6– 43 U/L). At screening, the patient reported regular consumption of 28 units of alcohol per week.

During the study treatment period, the patient developed back and shoulder pain and received a 2-week treatment course of diclofenac and ibuprofen. Shortly after completing this therapy, the patient was found to have an ALT of 151 U/L. After discontinuing the NSAID medications, the patient's ALT returned to normal at 35 U/L. The patient continued in the study taking "on demand" IC351 with no further abnormalities detected in liver function tests.

Patient 504-5236, who received treatment with 20 mg IC351, entered the trial with a mildly elevated ALT of 58 U/L and a reported consumption of 14 units of alcohol per week. At Visit 5, the patient reported to the investigator that he had recently increased

his alcohol consumption to 35 units per week. At Visit 5, his lab values demonstrated an increase in ALT of 230 U/L and AST of 84 U/L. His bilirubin was unchanged and remained normal at 9 mMol/L. The patient immediately decreased his alcohol consumption and both the ALT and AST levels were retested. Repeat analysis revealed both a normal ALT level at 41 U/L and a normal AST level at 29 U/L.

Medical officers Comments:

Clinically significant changes in chemistry or hematology values including the Changes in LFT's could not be directly related to the drug by this reviewer.

Vital Signs

According to the sponsor there were no statistically or clinically significant differences between the two treatment groups in the mean change from baseline to endpoint in any vital sign.

Medical officers Comments:

This reviewer agrees with the sponsors assessment.

Medical Officer's overall assessment of efficacy and safety:

In the opinion of this reviewer, the safety and efficacy data presented in Trial LVCQ shows the efficacy of IC351(20mg) for the treatment of erectile dysfunction, but this study was quite remarkable for unusually high incidence of drug related adverse events of headache in 36.6% and dyspepsia in 18.3% of the patients.

8.4.7 Time to onset Study LVCK:

Study LVCK assessed ——— and the patients used stopwatch methodology to determine the time following dosing at which 20 mg IC351 significantly improved patients' ability to engage in successful sexual intercourse. A total of 223 subjects were randomized among 10 centers in the United States (Placebo: N=74, 10 mg: N=74, and 20 mg: N=75). Virtually all subjects completed the trial. Patients took study drug when they began sexual activity and used a stopwatch to determine the time at which they achieved an erection sufficient for successful intercourse. The sponsor indicates that the first step down sequential test failure to reach a p-value of below .05 at 15 minutes. Thus, the sponsor's major conclusion is that " ——— after dosing as analyzed for the primary objective, and within 15 minutes after dosing by the Cox Regression Method".

Medical officers Comments:

- The statistical review showed that in the 20 mg group, 35% of the randomized patients never got a response in 30 minutes on any of the 4 doses taken during

the trial, furthermore placebo and 10mg group were indistinguishable with the respective percentages for the 10 mg and placebo groups being 43% and 51%. These results raise doubts about whether finding a "minimum time to response" is meaningful since minimum time that the drug takes to exert a pharmacodynamic effect was not considered. Additionally , by censoring data at 30 minutes, the sponsor lost an opportunity to assess the " true **median"** time to response, clearly a statistic with more potential clinical meaning. The distribution of this study data points were also quite variable raising further doubt about the median time of this variablity.

- Time to onset study results can be meaningfully apply to subjects who responded within 30 minutes for at least one dose.

8.4.8 The period of responsiveness LVDG

The duration of the period of responsiveness was also evaluated in a study LVDG assessing patients' ability to engage in successful sexual intercourse 24 hours and 36 hours following dose administration.
After a 4-week run-in period, subjects were stratified by numerical category of the Erectile Function Domain of the IIEF: mild: ED= 17-30, moderate: ED=11 -16, and severe: ED=1-10). Patients were then randomized into either of two sequences shown below. Patients were to attempt intercourse either 24 or 36 hours after dosing depending upon thc period of the study. There were 4 doses of either placebo or 20 mg tadalafil, 2 for each attempt time point (24 and 36 hours) after dosing. Subjects were instructed to take the two doses over approximately 2 to 3 weeks with each dose separated by 8-10 days.

Medical officers Comments:

- The major problem with the design of this study is that it assumes that the study patient. were "in response" for the full time before 24 or 36 hours. This study can only show that there was a percentage of patients in each group whose first attempt at intercourse after dosing was successful at 24 ***or*** 36 hours.
- The sponsor has demonstrated that the tadalafil and placebo groups can be statistically distinguished at 24 and 36 hours after dosing.
- Whether that result alone should be interpreted a demonstration of ——— ——— is very dubious. The trial was not designed to confirm that a response was taking place before the crossectional time points.
- Therefore the conclusion one can draw is , the percentage of "responders" in the tadalafil group at 36 hours is more like 40% rather than 60%.
- There is no PK/PD data to support this.

8.4.9. Miscelleneous Studies:

1. LVCF Study Summary:

A Randomized, Double-Blind, Comparison Study of IC351 (LY450190) and Sildenafil Administered "On Demand" to Patients with Erectile Dysfunction.

LVCF was a double-blind crossover study comparing 10 mg IC351 (market image formulation) and 50 mg sildenafil for "on demand" treatment of erectile dysfunction. Patients were instructed to take study medication at least 30 minutes prior to expected sexual activity. The study population consisted of men at least 21 years of age with erectile function of any severity and etiology. Fifty-seven patients were randomly assigned to either of the two treatment sequences. Fifty-three patients completed the study.

The primary efficacy objective of this study was to determine whether patients prefer 10 mg IC351 or 50 mg sildenafil for the treatment of ED. The relative efficacy of 10 mg IC351 and 50 mg sildenafil also was assessed.

The sponsors Conclusion: There was no significant difference in the percentage of patients who preferred 10 mg IC351 and those who preferred 50 mg sildenafil. Efficacy was similar between the treatments. The 10-mg dose of IC351 was non inferior to 50 mg sildenafil for the treatment of erectile function as assessed by the IIEF Erectile Function Domain.

Medical officers Comments:

This is an example of exploratory study.

2.LVCY Study Summary:

A Randomized, Double-Blind, Crossover Study of IC351 (LY450190) and Sildenafil Citrate for the Treatment of Patients with Erectile Dysfunction.

LVCY was a double-blind crossover study comparing 20 mg IC351 (market image formulation) and 50 mg and 100 mg sildenafil for "on demand" treatment of erectile dysfunction. Patients were instructed to take study medication at least 1 to 5 hours prior to expected sexual activity. The study population consisted of men at least 18 years of age with erectile function of any severity and etiology. Ninety-one patients were enrolled in the study. Eighty-four patients completed the study.

The primary efficacy objective of this study was to demonstrate that the efficacy of 20 mg IC351 is not inferior to 50 mg and 100 mg sildenafil in improving erectile dysfunction as assessed by the IIEF Erectile Function Domain.

The sponsors Conclusion: The 20-mg dose of IC351 was non inferior to 50 mg and 100 mg sildenafil for the treatment of erectile function as assessed by the IIEF Erectile Function Domain.

Medical officer's comment:

In this reviewer's opinion these studies capture a subjective choice and therefore exploratory in nature. 50mg and 100mg of sidenafil are commonly prescribed and they are marketed for a simple reason that there is a large spectrum of ED patients who need different doses. In case of IC 351, this reviewer considers that the patients should

be given a 10mg as a starting dose and titrated up if required. One drug unrelated death was notable in study LVCY. The patient had extensive coronary disease but one can unequivocally not rule out association with the drug.

8.5 Study drug and dose Response

Six pivotal studies were reviewed for dose selection. The responses to 3 primary endpoints for pivotal studies(**Study LVBK vs. Studies LVBN, LVCE, LVCE, LVCO, LVCQ, and LVDJ**) are summarized in Table 25 :

Table 25:Phase III Trials ,Combined Efficacy(Source Table ISE 4.23)

ALL	Placebo		IC_2.5mg			IC_5mg			IC_10mg*		IC_20mg*		
BASE	END	CHG	END	CHG	P	END	CHG	P	END	CHG	END	CHG	
IIEF													
12.1	12.2	0.1							19.3	6.4	18.7	7.3	LVBK
12.7	12.9	0.7	11.8	0.0	.993	17.1	4.9	.043	18.9	5.8	21.1	7.6	OTHERs
SEP2													
33.5	29.9	-4.1							56.7	22.2	54.4	22.6	LVBK
34.9	31.2	-2.4	31.2	4.2	.925	51.5	17.0	.037	62.7	23.5	64.6	30.7	OTHERS
SEP3													
16.8	20.0	1.9							48.0	28.4	41.8	29.1	LVBK
16.9	18.0	0.8	22.6	15.6	.441	36.2	22.7	.005	48.9	30.7	57.5	37.2	OTHERS

*P< .001

Summary by Treatment Group:

The response to the 2.5-mg IC351 dose was marginally better than placebo. The dose improved the IIEF Erectile Function Domain by less than four points. Overall percentage of successful sexual attempts on the 2.5-mg IC351 dose was only about 10% greater than placebo. GAQ did not demonstrate significant improvement.

The 5-mg IC351 dose significantly improved the IIEF Erectile Function Domain score and SEP Question 3 score in all primary efficacy studies. The SEP Question 2 score was Significantly improved in one of two studies with the 5-mg IC351 dose. Additionally, the 5-mg dose significantly improved several aspects of sexual satisfaction. The 5-mg IC351 dose also significantly improved the GAQ.

Both 10 mg and 20 mg IC351 significantly (statistically and clinically) improved all primary and secondary variables in all studies. The 20-mg IC351 dose provided greated improvement in erectile function, in subgroup of patients with severe ED, than the 10-mg IC351 dose. (Table 26)

Table 26: Efficacy by ED Severity , IIEF (Source Table ISE. 4. 5.)

Studies LVBN, LVCE, LVCO, LVCQ, and LVDJ(Pooled data for 5 studies)

Severity	Threshold	Placebo n (%)	IC 2.5mg n (%)	IC 5mg n (%)	IC 10mg n (%)	IC 20mg n (%)
IIEF						
MILD	All	114(100.0)	27 (100.0)	47 (100.0)	126(100.0)	128(100.0)
	Change > 0	43 (37.7)	20 (74.1)	35 (74.5)	100(79.4)	108(84.4)
	Change > 3	20 (17.5)	11 (40.7)	23 (48.9)	70 (55.6)	83 (64.8)
	Change > 6	11 (9.6)	6 (22.2)	12 (25.5)	37 (29.4)	50 (39.1)
	Change > 9	3 (2.6)	4 (14.8)	6 (12.8)	17 (13.5)	22 (17.2)
	Change > 12	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.6)
	Change > 15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MODERATE	All	72 (100.0)	16 (100.0)	32 (100.0)	83 (100.0)	49 (100.0)
	Change > 0	37 (51.4)	9 (56.3)	22 (68.8)	72 (86.7)	41 (83.7)
	Change > 3	33 (45.8)	9 (56.3)	18 (56.3)	63 (75.9)	39 (79.6)
	Change > 6	21 (29.2)	7 (43.8)	15 (46.9)	57 (68.7)	38 (77.6)
	Change > 9	14 (19.4)	5 (31.3)	12 (37.5)	49 (59.0)	34 (69.4)
	Change > 12	6 (8.3)	4 (25.0)	7 (21.9)	29 (34.9)	24 (49.0)
	Change > 15	1 (1.4)	0 (0.0)	2 (6.3)	11 (13.3)	12 (24.5)
SEVERE	All	109(100.0)	30 (100.0)	70 (100.0)	100(100.0)	68 (100.0)
	Change > 0	51 (46.8)	18 (60.0)	45 (64.3)	73 (73.0)	61 (89.7)
	Change > 3	26 (23.9)	10 (33.3)	27 (38.6)	60 (60.0)	49 (72.1)
	Change > 6	16 (14.7)	6 (20.0)	23 (32.9)	51 (51.0)	46 (67.6)
	Change > 9	12 (11.0)	4 (13.3)	15 (21.4)	44 (44.0)	42 (61.8)
	Change > 12	9 (8.3)	4 (13.3)	15 (21.4)	35 (35.0)	38 (55.9)
	Change > 15	3 (2.8)	3 (10.0)	10 (14.3)	32 (32.0)	34 (50.0)

As measured by SEP Question 3, the overall percentage of successful intercourse attempts was similar between all treatment groups in the treatment-free run-in period in all studies. The percentage of successful intercourse attempts was greater for the 20-mg IC351 treatment group in the range of ——— than for the 10 mg that was in the range of ——— The integrated analysis of SEP Question 3 data demonstrates that 74.7% of all post baseline attempts were successful for 20 mg IC351, compared with 60.9% for 10 mg IC351 and 31.9% for placebo. Both 10 and 20 mg doses achieved statistical and clinically meaningful improvement in majority of ED patients. 10 and 20mg doses significantly improved several aspects of ED, including ; Patients' overall erectile function, Patients' ability to achieve erections sufficient for vaginal penetration, Patients' ability to maintain erections for successful intercourse and Patients' and Partners' satisfaction with sexual intercourse.

Medical officer's comment:

In all studies 10 and 20 mg doses were significantly better than 2.5 and 5 mg respectively. The post treatment change from the base line values of primary efficacy variable IIEF between placebo and 10mg were similar across the studies utilizing 10mg dose (5.6-8.1; 5 studies). All studies showed clinically meaningful efficacy for 10mg dose. Additionally there was very little difference between 10 and 20mg (4studies) doses.
The post treatment change from the base line values of primary efficacy variable for SEP 2 for 10mg studies showed a range of This was comparable to the change observed in 20 mg studies .

The post treatment change from the base line values of primary efficacy variable for SEP 3 for 10mg studies showed a range of This was comparable to change observed in in 20 mg studies

The analysis of 3 studies where only 10and 20mg doses were used ,the efficacy was very similar .(Table 27)

If one considers the doubled exposure level of IC 351 in patients with mild to moderate renal failure and 25%>exposure in men over 65 years of age, 5mg may well be a good starting dose for many elderly patients and younger patients with renal compromise. These patients can be titrated up (and safety permitting) if needed.

This reviewer considers 5 OR 10 mg to be an effective starting doses for a vast majority of ED patients.

8.6. Assignment to study drug
A patient-randomization scheme was prepared for each severity stratum within each region. The randomization scheme was selected to strictly preserve blinding and was implemented at the study sites and by the Sponsor. The randomization scheme was performed by a computerized voice response system at a central location for all sites. All personnel, with the exception of a limited number of clinical trial materials personnel and supporting information services personnel, remained blinded to therapy codes until data lock.

Medical officer's comment:

The Drug assignments and blinding procedures were acceptable .

***8.7.* Treatment compliance**

The dosing regimen for this study was as needed, requiring no formal measure of compliance. The maximum dosing frequency allowed during the study was one dose daily. Patients were asked to return all used and unused study medication blister packs. Patients were to enter all doses taken in a patient diary (Sexual Encounter Profile), which were reconciled with the returned blister packs. Site personnel reviewed returned

blister cards to ensure that patients took a full (two-tablet) dose when taking the study medication. Accountability records were maintained at Visits 3, 4, and 5.

Medical officer's comment:
There were no compliance issues that should have a significant impact on the validity of data submitted and conclusions drawn.

8.8. Schedule of study assessments

These were described with the individual study reviews. The pivotal phase III studies had similar schedules .

8.9 Efficacy results:
The sponsors conducted 6 pivotal trials and sought 20mg as a proposed marketing dose. The pivotal studies in which 10mg , 20mg and placebo were used , both 10 and 20 mg were similar in their efficacy profile. Table 27.

Table 27:STUDIES LVBK,LVCO,LVDJ(BOTH 10/20 Used)

PH III	BASELINE BL	LVDJ(N253) CHANGE FROM BL		LVCO(N196) CHANGE FROM BL		LVBK(N216) CHANGE FROM BL	
END PT	RANGE	10	20	10	20	10	20
IIEF	[redacted]	6.6	8.0	8.1	8.0	6.4	7.3
SEP 2		21.3	21.3	34.5	35.3	22.2	22.6
SEP 3		32.8	29.0	47.9	49.7	28.4	29.1

8.10 Demographics

The demographics of the study populations in the primary efficacy studies of general populations were similar. Demographic characteristics evaluated include age, ED severity, ED etiology, ED duration, ethnic origin, smoking, alcohol use, presence of diabetes mellitus, body mass index, presence of depression, and presence of cardiovascular disease. Comparisons of demographic characteristics are drawn to the Massachusetts Male Aging Study (MMAS). Overall the patients of african descent were < 1% of the population in the pivotal studies.

Age: In addition to the mean age, the percentage of patients older than 65 years of age was similar among the treatment groups within individual studies as well as among studies. Table 28 provides the percentages of patients by age group (65 years of age and younger and older than 65 years of age) in each primary efficacy study in general

populations.

Table 28: Pivot Trials , Demographics(Age, Source Table ISE. 3. 2.)

	Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg	Total	AGE
	%	%	%	%	%	%	
LVBN	78.3		66.7	67.6		70.7	< 65
LVCE	81.6	70.3	77.2	78.5		76.9	
LVCO	62.1			60.0	56.9	59.7	
LVCQ	63.8				74.2	70.7	
LVDJ	74.0			71.8	68.0	70.8	
LVBN	21.7		33.3	32.4		29.3	
LVCE	18.4	29.7	22.8	21.5		23.1	>65
LVCO	37.9			40.0	43.1	40.3	
LVCQ	36.2				25.8	29.3	
LVDJ	26.0			28.2	32.0	29.2	

Ethnic Origin

Ethnicity was not an inclusion or exclusion criterion in clinical studies. In all studies except one (LVCO), Caucasians were the predominant ethnic origin. The ethnic distribution was otherwise similar among treatment groups and studies. Hispanics and African Americans were included in the clinical trials but the numbers were low. The patients of african descent were < 1% of the population in the pivotal studies. In Study LVCO, all patients were of East and Southeast Asian origin.

Presence of Cardiovascular Disease

In the general population primary efficacy studies, a large number of patients reported a history of cardiovascular disease. More than 25% of patients reported a history of hypertension in each study. Five to twelve percent of patients reported a history of coronary artery disease. The patients in the primary efficacy studies reported similar incidences of hypertension and heart disease to the MMAS population (hypertension 30% :coronary artery disease 12%).

Presence of Depression

In the general population primary efficacy studies, 2% to 8% of patients reported a history of depression. In the MMAS, 9% of patients reported depression.

Body Mass Index

According to the sponsor, the mean body mass index (BMI) was similar among the treatment groups in all of the primary efficacy studies. As expected, the BMI was lower

in Study LVCO, because the study was conducted in an Asian population in Taiwan. The LVCO results were more robust when compared to other studies. The mean BMI in these patients is similar to the mean BMI reported in the MMAS (27.5 kg/m 2).

Diabetes Mellitus

Patients with diabetes mellitus were included in each primary efficacy study. One study, LVBK exclusively enrolled patients with diabetes mellitus (Type 1 and Type 2). In the other primary efficacy studies, 12% to 25% of patients had diabetes mellitus.

Tobacco and Alcohol Use

The percentages of smokers in these studies are similar to the percentage of smokers (22%) reported by MMAS respondents. Most patients consumed alcohol. These patients also were approximately equally distributed among treatment groups, and in all studies except LVCO, most patients currently consumed alcohol. Table 29

Table 29: Pivot Trials , Demographics (Tobacco and Alcohol Use; Source Table ISE. 3. 8.)

Studies LVBN, LVCE, LVCO, LVCQ, and LVDJ

		Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg	Total
Currently Smokes		%	%	%	%	%	%
No	LVBN	78.3		77.8	79.7		78.6
	LVCE	88.2	83.8	84.8	78.5		83.8
	LVCO	62.1			66.2	63.1	63.8
	LVCQ	95.7				89.2	91.4
	LVDJ	78.0			78.6	88.0	82.2
Yes	LVBN	21.7		22.2	20.3		21.4
	LVCE	11.8	16.2	15.2	21.5		16.2
	LVCO	37.9			33.8	36.9	36.2
	LVCQ	4.3				10.8	8.6
	LVDJ	22.0			21.4	12.0	17.8

Erectile Dysfunction Etiology

Patients with ED of psychogenic, organic, and mixed etiology were included in the primary efficacy studies of the general population. Investigators assessed the etiology during the initial patient assessment. Most patients had an organic etiology or mixed etiology. The distribution of etiology was relatively balanced among treatment groups and studies.(Table 30)

Table 30: Pivtol Trials , Demographics Erectile Dysfunction Etiology

Studies LVBN, LVCE, LVCO, LVCQ, and LVDJ

		Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg	Total
Etiology of Erectile Dysfunction		%	%	%	%	%	%
Psychogenic	LVBN	17.4		15.3	8.1		13.5
	LVCE	5.3	8.1	5.1	6.3		6.2
	LVCO	10.6			6.2	9.2	8.7
	LVCQ	4.3				10.8	8.6
	LVDJ	8.0			4.9	11.0	7.9
Organic	LVBN	63.8		65.3	66.2		65.1
	LVCE	61.8	67.6	50.6	69.6		62.3
	LVCO	65.2			70.8	69.2	68.4
	LVCQ	44.7				39.8	41.4
	LVDJ	60.0			63.1	54.0	58.9
Mixed	LVBN	18.8		19.4	25.7		21.4
	LVCE	32.9	24.3	44.3	24.1		31.5
	LVCO	24.2			23.1	21.5	23.0
	LVCQ	51.1				49.5	50.0
	LVDJ	32.0			32.0	35.0	33.2

Erectile Dysfunction Duration

Most patients reported ED of at least1 year duration. The percentages of patients reporting ED of at least 1 year duration were similar within treatment groups in each study as well as among studies.

Erectile Dysfunction Severity

Erectile dysfunction severity was assessed by baseline scores of the IIEF Erectile Function Domain administered following the treatment-free run-in periods. Patients of all ED severities were included in the primary efficacy studies. Baseline ED severity is a good predictor of response. The mean baseline severity and distribution of patients in severity categories was similar among studies. See Table

Table 31: Pivot Trials , Demographics Erectile Dysfunction Severity (Source Table ISE. 3. 4.)

Studies LVBN, LVCE, LVCO, LVCQ, and LVDJ

Mean IIEF-EF Domain at Baseline	Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg	TOTAL
LVBN	14.5		13.8	14.3		14.2
LVCE	13.3	13.3	12.4	14.6		13.4
LVCO	15.5			14.4	17.0	15.6
LVCQ	14.3				16.2	15.5
LVDJ	15.0			14.6	15.1	14.9

Medical officer's comment:

Most of these trials were conducted outside of the North america. The sponsors attempted to balance the patients in demographics and ED spectrum among the patients across the studies .There was a low participation of the patients of african descent (<1%) in pivotal trials.

8.11 Conclusions regarding demonstrated efficacy

The studies of doses 2.5 mg and 5 mg did not conclude as positive trials although 5 mg dose failed only marginally in one primary end point (SEP 2; p=.064). Doses of 10 mg and 20 mg IC351 improved all primary and secondary variables in all primary efficacy studies with statistical and clinical significance. The clinical pharmacology review concluded that in elderly (>65) patients the exposure to this drug was increased by a tleast 25 % and that the patients with mild to moderate renal failure show that the exposure levels were doubled. The pharmacometric models also showed that beyond 10 mg dose there was a little additional effect that can be achieved and curves tend to plateau just beyond 10 mg dose. These facts demonstrate that a starting dose for a large majority of patients should be 5 mg OR 10 mg with the option to tirate up with in the confines of safety margins . The individual pivotal trial safety review demonstrated dose related trends in the incidence of treatment related adverse events like headache, backpain and dyspepsia.

[redacted]. The period of effect also can only achieve limited iteration in the label as it too had deficiency because it assumed a presence of effect before 24 hours. In the study, a proportion of those patients who showed effect at 24 hours did have effect at 36 hours. This was not looked at, by the sponsor. There is no PK/PD correlation in this study either.

8.12 Achievement of protocol defined primary efficacy endpoints

Although the sponsors seek 20 mg dose their phase III studies showed clinical and statistical efficay for 10mg and 20mg doses in all of the primary variables tested in the

pivotal trials. Additionally 5 mg dose showed clinically significant improvement in the ED of the studied patients.

8.13 Medical officer's overall assessment of efficacy

Doses of 10 mg and 20 mg IC351 statistically and clinically significantly improved all primary and secondary variables in all primary efficacy studies. The 5-mg IC351 dose significantly improved all primary variables in one primary efficacy study and two of three primary variables in another primary efficacy study. The 5-mg dose also provided statistically significant improvement in most secondary variables. 5 and 10mg showed a better safety profile than 20 mg. There fore 5 mg and 10 mg doses should be the starting dose in majority of patients with an option of up titrate. Clinically significant improvement was noted in all of the following variables for doses of 10 mg to 20 mg IC351.

1. Patients' overall erectile function
2. Patients' ability to achieve erections sufficient for vaginal penetration
3. Patients' ability to maintain erections for successful intercourse
4. Patients' satisfaction with sexual intercourse
5. Patients' overall satisfaction
6. Patients' satisfaction with the hardness of their erections
7. Patients' confidence in their ability to attain and maintain an erection
8. Partners' satisfaction with sexual intercourse.

8.14 Support of efficacy claims in proposed label

1. 10 vs 20mg Doses: 10mg data supports it for a starting dose claim. 20 mg dose is not approvable at this time due to outstanding safety concerns (Nitrate, Renal function\ and QTc data)
2. The data provided supports 5 mg OR 10mg as a starting dose in many healthy younger patients, elderly and patients with mild and moderate renal failure.
3. Onset : Only a limited factual statement can be entered into label contrary to the sponsors claim.
4. Duration of effect : Only a limited factual statement can be entered into label contrary to the sponsors claim.

9. Integrated review of safety

9.1. Data sources

The focus of safety review was pivotal studies, controlled studies including LVCR, Clinical pharmacologic and PI and PII studies, long term exposure studies and special studies for CVS, SPERM and VISUAL function effects of IC351.Table32 list some of the important safety studies. All other individual studies CRF/CRT, ISS and other submissions were reviewed for safety.

Table 32: Studies Included in the Integrated Summary of Safety

Study Grouping	Studies
Primary placebo-controlled integrated database	LVBN, LVCE, LVCQ, LVCO, LVDJ, LVBK
Open-label, long-term safety studies	LVBD, LVBL(ONGOING), LVDR
Clinical pharmacology studies	40^{+} completed, Some Ongoing
Period of responsiveness studies	LVBJ, LVCK, LVDG
Studies with active control	LVCF, LVBO, LVCY

9.2. Description of patient exposure

More than 4000 subjects received at least one dose of IC351. In clinical trials, patients were exposed to IC351 for up to 21 months. All At-home "On-Demand" Market Image Formulation Studies including; LVBK, LVBN, LVCE, LVCO, LVCQ, LVDJ, LVBO, LVCK, LVDG, LVCF, and LVCY. This pooling included 1561 IC351-treated patients and 758 placebo-treated patients from *studies* and part important part of the safety data base. In the open-label, long-term safety studies LVBD, LVDR and LVBL, 800 patients were exposed to at least 20 mg of the market image formulation or its equivalent for 6 months, of whom 691 patients were exposed to 20 mg of the market image formulation for 6 months Over 500 patients were exposed to at least 20 mg of the market image formulation or its equivalent for 1 year, of whom over 100 patients were exposed to 20 mg of the market image formulation for 1 year.(see table33)

Table 33: Patient Year Exposure IC 351 P2,3& Open Label Studies

Patient-Year Exposure to IC351
By Duration of Study
Phase 2, Phase 3 and Open-Label Studies

	Number of Studies	Number of Patients	Total Patient Years
Studies with <1 month duration	7	862	
Studies with 1 month to 6 months duration	13	1869	384.4
Open-Label, Long-Term Studies (>6 month exposure)	2	1376	1155.0
		Total =	1539.4

Medical officer's comment:
The number of patients exposed to the Cialis™, and the duration of its exposure, in conjunction with the historical information relevant to other PDE 5 inhibitors, is considered adequate and consistent with ICH guidelines to assess the general safety of Cialis™ for the indication of management of Erectile Dysfunction in men.

9.3. Safety assessments conducted in the safety studies

9.3.1. Procedures for collecting safety data

According to the sponsors submission; in each of the studies, patient demographics (e.g., racial origin and age) were recorded at Visit 1. All studies collected other clinical characteristics (e.g., ED etiology) at Visit 1. Routine safety data (adverse events, vital signs, and clinical laboratory tests) were monitored throughout the studies. In addition, ECG data were collected for all studies at Visit 1 and end of study.

Adverse events were elicited by open-ended, non directed questioning of the patients, clinical observation, and source document review. Adverse events were classified using the Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART) dictionary for uniformity of reporting. In addition, information about concomitant medication use was recorded at each visit. Serious adverse events were to have been reported to the sponsor within 24 hours of the initial report. When a patient discontinued the study, the reason for discontinuation was recorded. Vital signs (diastolic and systolic blood pressure, and heart rate) were measured at all visits for all studies.Clinical laboratory tests (serum chemistry, hematology) were performed at all visits for all the studies. Urinalysis was obtained at the screening and final visits. A central contract laboratory, [redacted] assayed all the samples for all studies.

For all completed studies, the last patient visit date was 19 April 2001. For all ongoing studies, deaths were reported up to 28 May 2001. For ongoing studies LVCQ, LVBL, and LVCZ, serious adverse events are reported up to the last patient visit date for the interim database lock. For study LVDR, serious adverse events are reported up to 02 April 2001. Last safety update was sent in March 2002, for approximately 235 new patients who had been exposed to IC351 since the original NDA, but were not inlcuded in the 4-month safety update because interim datalocks had not been planned. This update included safety information from studies LVCR, LVDR, and LVBL and was also reviewed.

Medical officer's comment:

Safety assessments conducted in the safety studies and Procedures for collecting safety data and their submission were adequate.

9.3.2. Analysis and reporting of safety data

Safety analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patient 117-9703 in study LVBK, who had a myocardial infarction after randomization to IC351, but did not take any study drug, was, however, not reported as having had a serious adverse event in the IC351-treated group.

For all continuous safety measurements, treatment-group differences in change from baseline to endpoint were analyzed by an analysis of variance (ANOVA) containing the terms of treatment and protocol. Because the continuous safety measurements (laboratory values, vital signs, and ECG) were generally not normally distributed, inferences were based on the analyses of ranked data. Baseline measure was the last available measure of Visit 1 and Visit 2, and endpoint measure was the last available measure among the postbaseline visits in the reporting interval. Only the patients who had a baseline and at least one postbaseline measurement were included in the analysis of mean change. Comparisons among the treatment groups were made using least square means with type III sum of squares. For analysis of proportions, incidence rates were compared among treatment groups by a Cochran-Mantel-Haenszel (CMH) general association test adjusting for protocol, a Fisher's exact test, or a Chi-square test. All reported p-values were based on two-sided tests. Results were reported as statistically significant if a p-value of <0.05 was obtained.

Medical officer's comment:

Assessments, analyses and reporting methods are adequate and appropriate for this product.

9.3.2.1. Adverse events (Overall Assesment)

Adverse events associated with IC351 administration include headache, dyspepsia, back pain, myalgia, nasal congestion, and flushing. In the placebo-controlled, market image formulation, "at home" studies headache (11%), dyspepsia (7%), back pain (4%), myalgia (4%), nasal congestion (4%), and flushing (4%) were the most frequent events in the IC351-treated group. The association of these events with IC351 and of PDE5 inhibitors is plausible. Dyspepsia, is thought to result from relaxation of lower esophageal smooth muscle tone by inhibition of PDE5. Headache, nasal congestion, and flushing can all be due to vaso dilatation. However the mechanism for back pain and myalgia, is unknown. This presents a unknown safety risk in patients with diminished renal patients and the elderly and may be due to long sojourn of the drug in the body and associated increased exposure to its metabolite. Adverse events were generally mild to moderate in intensity with some exceptions.

In the placebo-controlled, phase III studies 27 patients (2.0%) discontinued due to

adverse events, 5 of 379 patients (1.3%) in the placebo group and 22 of 949 patients (2.3%) in the IC351-treated group. The discontinuation rate (3.6%) in 20 mg group (N=330) was twice (1.5%) as much as the 10 mg (N=394). Discontinuations due to adverse events in three long-term, open-label studies, LVBD, LVBL and LVDR were 4.4% , 5.4% and 5.7 % respectively.

In the primary placebo controlled Phase 3 database, serious adverse events were reported by 15 patients. In the IC351-treated group, 9 of 949 patients (0.9%) reported at least one serious adverse event compared with 6 of 379 (1.6%) of placebo-treated patients.

9.3.2.2. Deaths

As of 28 May 2001, a total of 7 deaths were reported from among more than 4000 subjects who received IC351 . Of these deaths, 1 was in study LVCY and 6 were in study LVBL as of march 2002 when the last safety update was submitted. The review of CRF on death cases did not directly attribute these to the drug.

9.3.2.3. Vital signs And Cardiovascular Safety

Reader is also referred to special safety section. Sexual activity by itself, as a result of demands placed on the cardiovascular system, is associated with a risk for cardiovascular events, especially in patients with underlying cardiac disease. Hence, the cardiovascular assessment of IC351 included an evaluation of the effects of IC351 on hemodynamic parameters as well as the monitoring and analysis of cardiovascular adverse events.

The effect of IC351 (administered alone or in combination with antihypertensive medications) on blood pressure and heart rate, Co-administration of IC351 with nitrates and hemodynamics, IC351 effect on electrocardiograms (ECG), including QTc interval, assessment of cases of hypotension or postural hypotension resulting in syncope attributable to IC351 administration, incidence of myocardial infarction compared with general population.

ECG Data:

Change of ECG parameters from baseline to endpoint were compared between treatment groups using ANOVA. Electrocardiogram abnormalities were also evaluated by examining the proportion of patients who were normal at baseline but had abnormal traces at their final visit, within abnormality categories specified a priori. The proportions were compared between treatment groups by a Fisher's Exact test. The categories of electrocardiogram abnormality were as follows: axis abnormality, conduction disturbance, ischemia, morphology abnormality, myocardial infarction, supraventricular rhythm disturbance, ventricular rhythm disturbance, other rhythm disturbance, ST segment abnormality, and T wave abnormality. The proportions of patients who were abnormal at baseline but had normal traces at their final visit were also presented

Medical officer's comment:

Vital and Cardivascular assessments are appropriate for this class of drugs.
A cadiorenal consult reported no obvious QTc prolongation attributable to the drug from the analysis of the submitted data with a maximum dose of 40 mg . However this dose (40mg) does not have a wide enough safety margin if 20mg is the only dose sought.

9.3.2.3. Vision Safety

Effects of IC351 on vision were tested in two clinical pharmacology studies, LVAN and LVC N. Both studies were double-blind, randomized studies in healthy subjects, where the following tests of vision were performed before and after dosing with IC351.

- The Farnsworth-Munsell (FM) 100-hue test of color vision
- Visual field test
- Sight assessments: distant vision, near vision, visual co-ordination, and refraction
- The Flash Ganzfeld full-field electroretinogram (ERG). The ERG was recorded according to the recommendation of the International Society for Clinical Electrophysiology of Vision
- Examination of the anterior and posterior segments of the eye
- Measurement of intraocular pressure

These studies showed that single doses of 10 mg or 20 mg IC351 had no effect on vision, including color vision and electroretinograms. IC351 did not increase intraocular pressure. Of more than 4000 subjects who received IC351, only three reported color vision abnormalities.

Medical officer's comment:
The special safety studies performed in this trial are appropriate for this class of drugs. These studies were submitted for an FDA opthalmology consult. The following summarizes their view:

- Multiple deficiencies identified.
- Potential for visual abnormalities was deemed to be the same as sildenafil and label should be amended to reflect that .
- 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).

9.3.2.5. Sperm Studies:

In animal toxicology studies, dogs given IC351 for 6 months and 12 months were foundon histopathological examination to have testicular alterations characterized by hypospermia whose severity and degree were time-related and exposure-related. This effect was tested in human studies.
In Study LVCD : 10 mg dose was tested (N=204)x6 months.
In Study LVCZ: 20 mg dose was tested(N=217)x 6months
The primary safety variable for this study was the proportion of subjects with 50% or more reduction in sperm concentration from baseline. The primary analysis was to

determine whether the IC351 treated group was non-inferior to the placebo treated group at 6 months post-dosing.

Medical officer's comments:

- The primary variable used is appropriated in these studies LVCD and LVCZ to test the early and intermediate effect on germ cells, sperms and semen parameters.
- The special safety studies performed in this trial were in conformance with the division's policy.

9.3.2.6. Clinical laboratory tests

Clinical Laboratory Data

Clinical laboratory tests were grouped into the categories of serum chemistry (including liver function tests), hematology, and urinalysis.

- Serum Chemistry: blood urea nitrogen (BUN), creatinine, random glucose, calcium, phosphorus, uric acid, sodium, potassium, chloride, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, total protein, cholesterol, and albumin,
- Hematology: hemoglobin, hematocrit, erythrocyte count, mean cell volume (MCV), red blood cell morphology, leukocyte count, segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands, and platelet count.
- Urinalysis: pH, protein, glucose, urobilinogen, occult blood, and microscopy.

Summary statistics were calculated for baseline, endpoint, and change from baseline of each continuous laboratory variable. Differences between the IC351 and placebo groups in the mean change from baseline to endpoint were analyzed using ANOVA.

The proportions of patients with high, low, or abnormal laboratory values based on Lilly reference ranges at any time while on treatment were compared among the treatment groups using a Fisher's Exact test.

Medical officer's comment:

Labaratory and Safety assessments listed are adequate and appropriate for this product.

9.4. Demographics (for Pivotal and supportive Studies)

The primary placebo-controlled phase 3 integrated database comprises pooled data from six studies – LVBN, LVCE, LVDJ, LVCQ, LVCO and LVBK.

The study designs were similar for all six studies. In each study, patients were treated for 12 weeks with placebo or IC351. Complete 3-month data from the 6-month study LVCQ was incorporated for this analysis . The market image formulation was used in all studies with doses ranging from 2.5 mg to 20 mg. In four of the six studies (LVCO, LVDJ, LVCQ, and LVBK) the proposed dose of 20 mg was included. Patients were instructed to take one dose prior to anticipated sexual activity and to take no more than one dose per day. These studies included a diverse global population from different countries (Argentina, Australia, Canada, Mexico, Spain, and Taiwan).Patients with ED who all had preexisting diabetes mellitus formed the patient population for study LVBK.

According to the sponsor, the patient demographics were similar across the studies with regard to age, body mass index, history of smoking, and associated medical conditions such as hypertension, diabetes mellitus, and heart disease. There were no statistically significant differences in patient characteristics and demographics between the placebo and the combined and integrated IC351 treatment groups .
The population of study patients were men 18 years of age or older with a history of erectile dysfunction of at least 3 months duration. Patients with different etiologies and all degrees of severity of erectile dysfunction participated in these studies.
Caucasians constituted 80% of the total population, East or Southeast Asian 15%, Hispanic 3%, and men of African descent and Western Asians constituted 1% each.
The mean age of patients in these studies was 58 years, and the ages ranged from 22 to 82 years. The mean weight at baseline was 84 kg. The mean body mass index (BMI) was 28 kg/cm^2.
At baseline, 23% of patients were smokers, 63% consumed alcohol at a mean intake of 4.8 units per week, 34% had a history of diabetes mellitus, 31% had a history of hypertension, 7% had a history of coronary artery disease, and 5% had a history of depression. The percentage of patients with diabetes mellitus was higher in the placebo, 10 mg and 20 mg IC351 groups compared to the 2.5 and 5 mg IC351 groups because only the 10 mg and 20 mg IC351 doses were used in study LVBK in which all patients had diabetes mellitus. A total of 1328 patients were randomized to treatment in the pivotal phase 3 studies.

The following groups of patients were not included in these studies:

-Patients with myocardial infarction within the last 90 days

-Patients with unstable angina or angina occurring during sexual intercourse

-Patients with New York Heart Association Class 2 or greater heart failure in the last 6 months

-Patients with uncontrolled arrhythmias, hypotension (<90/50 mm Hg) or uncontrolled hypertension

-Patients with a stroke in the last 6 months

-Patients with clinically significant renal disease

-Patients with clinically significant hepatobiliary disease as evidenced by AST or ALT >3 times the upper limit of normal

-Other concomitant treatment for erectile dysfunction

Please also refer to Efficacy section 8 of this review.

Medical officer's comment:

The demographics, in general , mimics the spectrum of the ED population in the US with an exception of lower percentage (<1%) of patients of african descent.

Weight was a variable in the PK/PD clinical pharmacology studies , the efficacy results in the study LVCO done in Taiwan showed robust responses when compared to other pivotal studies.

9.5. Adverse events and Special safety considerations

9.5.1. Market image formulation , At Home (MIFAH) safety Studies : (LVCE, LVBN,LVCO, LVCQ, LVBK, LVDJ, LVCK, LVCY, LVBO, LVCF, LVDG)

9.5.1.1 Treatment-Emergent Adverse Events

The most frequently reported adverse events associated with IC351 administration were headache, dyspepsia, back pain, myalgia, nasal congestion, and flushing. These events were mild or moderate in most patients, generally transient, and the percentage of patients reporting adverse events decreased with continued dosing. Other events for which a relationship to study drug was uncertain but plausible were swelling of eyelids, sensations described as eye pain or eye pressure, and conjunctival hyperemia . These events each occurred at a frequency of less than 1%. No cases of priapism were reported. Table (34)

Table 34: Market image formulation At home safety Studies, Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events Occurring in >2% of IC351-Treated Patients Pooled Market Image Formulation At-home Studies(Source :Table H 21 Summary)

Event	IC351 (N=1561)	Placebo (N=758)
	(%)	(%)
Headache	11	4
Dyspepsia	7	1
Back pain	4	3
Myalgia	4	1
Nasal congestion	4	2
Flushing	4	1

Medical officer's comment:

The adverse events are plausible with this drug and similar to the ones obtained across the other studies.

9.5.1.2 Serious adverse events

Serious adverse events were reported in 12 of 1561 (0.8%) IC351-treated patients and 7 of 758 (0.9%) placebo-treated patients in the the pooled data . In sponsors assessment none of the serious adverse events were related to study drug.

Medical officer's comment:

The serious adverse event rates were similar between the placebo (7/758=.92) and the IC 351 (12/1561=.77). This reviewer agrees with the sponsor that none of these events were directly attributable to the study drug.

9.5.2.3 Deaths

There was one death reported study LVCY , in this data base of over 2000 patients. Patient 602-6077, who began treatment with 20 mg IC351 on 5-Jan-01, experienced cardiac arrest on 23-Jan-01, which resulted in death during the study. The 35 year old patient had a past history of hypercholesterolemia [1998], diabetes mellitus [1996], and obesity, with a body mass index of 39.4 kg/m^2.
The patient was exercising for the first time in several years and collapsed after about 15 minutes of working out on a treadmill. He immediately received cardiopulmonary resuscitation (CPR), and when medics arrived he was in full cardiac arrest. Medics provided advanced cardiopulmonary life support, administered epinephrine, atropine, lidocaine, and counter shocked seven times. The patient never responded to resuscitation and was dead upon arrival to the hospital emergency room. An autopsy reported up to 80% narrowing of anterior descending artery, up to 80% narrowing of predominant circumflex artery, up to 90% narrowing of small right artery, and left ventricular hypertrophy. The autopsy confirmed that the death occurred from a pre-existing condition of coronary atherosclerosis (coronary artery disorder). The patient's widow could not find the patient's drug administration diary. She does not know how many doses of study drug the patient took, but she thinks his last dose was about 45 minutes prior to going to the gym on the day of his death. The investigator reported the event as unrelated to study drug or protocol procedures.

Medical officer's comment:

The death report was reviewed for causal relationship with the IC351. This patient's autopsy report showed an extensive coronary disease. He had the risk factors for this

event. While direct attribution to the drug cant be made , it is difficult to rule out the relationship .

9.5.1.4. Premature discontinuations due to adverse events

In all controlled studies in which IC351 was used as market image formulation and taken at-home as needed, 1.7% of IC351-treated patients and 1.1% of placebo-treated patients discontinued due to adverse events.

Medical officer's comment:
Adverse events of Headache, dyspepsia , back pain and flushing were associated with discontinuation of treatment in some patients. This was also seen in other studies.

9.5.2 Phase 3 Integrated Safety Database

9.5.2.1 Exposure

The primary placebo-controlled phase 3 integrated database comprises pooled data from six multicenter studies, conducted in various countries (Argentina, Australia, Canada, Mexico, Spain, and Taiwan) - LVBN, LVCE, LVDJ, LVCQ (3-month interim), LVCO,and LVBK. A total of 1328 patients were randomized to treatment in these phase 3 studies. The characteristics of patients in these clinical studies was similar with respect to age, body mass index, smoking history, and underlying medical conditions such as hypertension, diabetes mellitus, and heart disease.

The study designs were similar for all six studies. In each study, patients were treated for 12 weeks with placebo or IC351. Complete 3-month data from the 6-month study LVCQ was submitted. The mean length of study participation was approximately 90 days. Patients took a mean of 25 to 30 doses in different treatment groups during the studies, which translated to a mean of approximately 2 doses per week shows the exposure to study drug in patient-years. Patients were exposed to placebo for 90 patient-years and to IC351 for 229 patient-years.

9.5.2.2 Patient Disposition

Most patients (89.2%) completed the 12 weeks of treatment prior to their study termination visits . There were no statistically significant differences in discontinuations due to adverse events among treatment groups (p=0.069). Patients who continued in the study beyond the 3-month visit for LVCQ Were classified as completing the study.

Overall, 144 patients (10.8%) discontinued from the studies. The most common reason for not completing the studies was personal conflict or other patient decision (37 patients, 2.8%). 27 patients (2.0%) discontinued due to adverse events (5 of 379 patients (1.3%) in the placebo group and 22 of 949 patients (2.3%) in the IC351-treated group.

9.5.2. 3 Treatment-Emergent Adverse Events :

In the IC351-treated patients, 540 of 949 (56.9%) reported at least one treatment-

emergent adverse event compared with 181 of 379 (47.8%) placebo-treated patients. Headache, dyspepsia, back pain, myalgia, rhinitis (nasal congestion), and vasodilatation (flushing) occurred in greater than 2% of the IC351-treated patients and were more frequent than in placebo-treated patients. These events were generally lower in the 2.5 mg and 5 mg dose groups, and varied in incidence between studies. The following adverse events occurred in greater than 2% of the IC351-treated patients but were similar or lower in frequency compared with the placebo-treated patients: infection, pain, flu syndrome, dizziness, cough increased, pharyngitis, and surgical procedure.

When adverse events were analyzed for degree of maximum severity in the all IC351-treated group , only 7.8% of all IC351 treated patients had a severe treatment-emergent adverse event compared with 6.1% of placebo treated patients. The majority of treatment-emergent adverse events in IC351-treated patients (466 of 540 (86.3%)) were mild or moderate. Of the patients who experienced headache, 116 of 127 (91.3%) had maximal severity reported as mild or moderate. Of the patients who experienced dyspepsia, 91 of 97 (93.8%) had maximal severity reported as mild or moderate. Of the patients who experienced back pain, 46 of 55 (83.6%) had maximal severity reported as mild or moderate. Of the patients who experienced myalgia, 42 of 45 (93.3%) had maximal severity reported as mild or moderate. Of the patients who experienced nasal congestion, 38 of 41 (92.7%) had maximal severity reported as mild or moderate. Of the patients who experienced flushing, 33 of 35 (94.3%) had maximal severity reported as mild or moderate. The percentage of patients reporting these events decreased with continued dosing during subsequent visits for all these adverse events Table 35:

Table 35: Pivotal StudiesTreatment-Emergent Adverse Events

	Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg	ALLIC
	(N=379)	(N=74)	(N=151)	(N=394)	(N=330)	(N=949)
Event Classification	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PATIENTS WITH >= 1 EVENT	39 (10.3)	14 (18.9)	19 (12.6)	111 (28.2)	115 (34.8)	259 (27.3)
PATIENTS WITH NO EVENTS	340 (89.7)	60 (81.1)	132 (87.4)	283 (71.8)	215 (65.2)	690 (72.7)
HEADACHE	8 (2.1)	4 (5.4)	10 (6.6)	39 (9.9)	45 (13.6)	98 (10.3)
DYSPEPSIA	4 (1.1)	1 (1.4)	2 (1.3)	31 (7.9)	37 (11.2)	71 (7.5)
VASODILATATION	6 (1.6)	1 (1.4)	2 (1.3)	13 (3.3)	15 (4.5)	31(3.3)
MYALGIA	2 (0.5)	2 (2.7)	1 (0.7)	13 (3.3)	14 (4.2)	30(3.2)
BACK PAIN	2 (0.5)	1 (1.4)	1 (0.7)	8 (2.0)	16 (4.8)	26 (2.7)
RHINITIS	2 (0.5)	2 (2.7)	2 (1.3)	12 (3.0)	5 (1.5)	21 (2.2)
DIZZINESS	3 (0.8)	1 (1.4)	2 (1.3)	6 (1.5)	6 (1.8)	15 (1.6)
NAUSEA	1 (0.3)	0	0	4 (1.0)	5 (1.5)	9 (0.9)
PAIN	0	0	0	7 (1.8)	1 (0.3)	8 (0.8)
DIARRHEA	0	0	0	3 (0.8)	3 (0.9)	6 (0.6)
ABDOMINAL PAIN	0	0	2 (1.3)	1 (0.3)	2 (0.6)	5 (0.5)
EYE PAIN	0	0	0	2 (0.5)	3 (0.9)	5 (0.5)
VOMITING	0	0	0	3 (0.8)	2 (0.6)	5 (0.5)
AMBLYOPIA	2 (0.5)	0	0	1 (0.3)	3 (0.9)	4 (0.4)
ASTHENIA	0	1 (1.4)	0	2 (0.5)	1 (0.3)	4 (0.4)
PALPITATION	1 (0.3)	0	0	2 (0.5)	2 (0.6)	4 (0.4)
UNEXPECTED BENEFIT	0	0	0	1 (0.3)	3 (0.9)	4 (0.4)
ABNORMAL VISION	0	0	1 (0.7)	2 (0.5)	0	3 (0.3)
ARTHRALGIA	0	0	0	2 (0.5)	1 (0.3)	3 (0.3)

Medical Officers Comments:

The treatment emergent adverse event data in phase three trials is quite similar across the studies. In some studies patient discontinuation due these events were dose related.

9.5.2.4 Deaths :

There were no deaths reported in these studies as of 28 May 2001.

9.5.2. 5. Serious Adverse Events:

A total of 15 patients randomized to treatment in these studies each reported a minimum of one serious adverse event after randomization. Of the IC351-treated patients, 9 of 949 patients (0.9%) reported a minimum of one serious adverse event after randomization compared with 6 of 379 (1.6%) for placebo-treated patients. Of note, 2 patients in the placebo-treated group experienced myocardial infarctions, whereas no patients in the IC351-treated group experienced a myocardial infarction.

Patient 117-9703 in study LVBK, who was randomized to 20 mg of IC351, reported a myocardial infarction after randomization, but prior to his taking any study drug. As it was verified that he had not taken any study drug, this patient's case did not satisfy formal pre-specified criteria for reporting as a serious adverse event that sponsor followed at the time of the study. Therefore, this event was not included in the list of serious adverse events .

Patient 024-2152 in study LVDJ experienced a serious adverse event of angina pectoris between Visit 1 (entry) and Visit 2 (randomization). This event was classified as serious according to the formal pre-specified criteria for reporting a serious adverse event that the sponsor followed at the time of the study (which changed after study LVBK was completed). This event does appear in the listing of serious adverse events , but does not appear in Table which summarizes serious adverse events that occurred after randomization. *None of the serious adverse events reported were causally related to IC351 administration.*

Medical Officer's Comments:

The reviewer agrees with the sponsors assessment of these serious adverse events.

9.5.3 Study LVCR

Study LVCR was a multicenter, double-blind, randomized, placebo-controlled, parallel design study designed to evaluate the efficacy and safety of "on-demand" dosing of 20 mg IC351 or placebo administered for 12 weeks to men with erectile dysfunction (ED).

This study was conducted in the United States, and included the same endpoints that were used in the pivotal Phase 3 studies included in the NDA. According to the sponsor,

for this study, all last patient visits have occurred, all the data have been collected and locked, and all safety data analyses have been completed.

9.5.3 .1 Treatment-Emergent Adverse Events

According to the sponsor , the most frequently (5%) reported treatment-emergent adverse events in IC351-treated patients included headache (8.9%) and pain (6.2%). The only adverse event for which the difference in frequency between IC351-treated patients and placebo-treated patients was statistically significant was headache (p = 0.041).

Table 36: Treatment-Emergent Adverse Events >2%:LVCR

Event Classification	Placebo (N = 49)		20 mg IC351 (N = 146)		p-Value
	n	%	n	%	
Headache	0		13	8.9	0.041
Pain	1	2.0	9	6.2	0.456
Dyspepsia	0		7	4.8	0.195
Infection	0		6	4.1	0.340
Myalgia	0		5	3.4	0.333
Diarrhea	0		4	2.7	0.574
Rhinitis	0		4	2.7	0.574

Medical Officers Comments:

The adverse events seen in LVCR are similar to those noted in the review of Phase 3 pivotal studies

9.5.3.2 Discontinuations Due to Adverse Events

Table 37 provides the discontinuations due to non-serious adverse events for Study LVCR. Eight patients discontinued due to non-serious adverse events. Of these, 7 patients were in the IC351 treatment group and 1 patient was in the placebo treatment group. In addition, as described in the next section (Serious Adverse Events), Patient 814-8510 who had a brain tumor that required surgery and chemotherapy was also discontinued from the study.

Table 37:Discontinuations Due to Non-Serious Adverse Events LVCR

Subject ID	Event Classification	Study Drug
803-8198	Myalgia	20 mg IC351
806-8285	Dyspepsia	20 mg IC351
810-8394	Abdominal pain	20 mg IC351
810-8396	Myalgia	20 mg IC351
812-8460	Pain	20 mg IC351
810-8392	Angina pectoris	20 mg IC351
813-8485	Back pain	20 mg IC351
813-8486	Pain	Placebo

Patient 810-8392 was a 65 year old Caucasian man randomized to 20 mg IC351 who was discontinued after he took nitrates for an episode of angina pectoris. This patient had a past history that included angina pectoris, myocardial infarction, hyperlipemia, and hypertension. Medications on entry into study included acetylsalicylic acid, atorvastatin, tocopherol, trandolapril, and amlodipine besylate. After enrolling in the study and starting study medication (first dose taken two days prior to the event), the patient informed the study coordinator, who had called him to return for a laboratory test, that he had had chest pain and had self-medicated with nitroglycerin. He had not informed the site previously of having nitrates in his possession for possible future use. The patient's chest pain had subsided and prior to this telephone conversation. He had taken two additional doses of study drug without recurrence of chest pain. The patient was discontinued from the study and the patient was instructed to contact his cardiologist for further management of chest pain. The investigator assessed the event as related to study drug. Because the patient had a prior history of coronary artery disease and angina pectoris and had nitrates to treat this condition, and because re challenge with study medication did not result in recurrence of his symptoms, the Sponsor assessed the event as unrelated to study drug.

Medical Officers comments:

The reviewer agrees with the sponsors inference .

9.5.3 .3 Serious Adverse Events

Four patients experienced serious adverse events in this study. No deaths occurred in this study. Of the 4 patients who experienced a serious adverse event, 3 were being treated with 20 mg IC351 and 1 was taking placebo. Patient 814-8510 discontinued from the study due to a serious adverse event. Table 38 lists the serious adverse events reported during this study.

Table 38: Serious Adverse Events. LVCR

Subject ID	Event Classification	Study Drug	Possible Relationship to Study Drug
804-8217	Carotid occlusion	20 mg IC351	No
814-8510	Neoplasm	20 mg IC351	No
804-8210c	Chest pain	Placebo	No
817-8600c	Esophagitis	20 mg IC351	No

Patient 817-8600 was a 58 year old Caucasian man randomized to 20 mg IC351 who was hospitalized during the study for chest pain and was diagnosed to have esophageal spasm. This patient had a past history that included hyperlipemia, hypertension, and gastroesophageal reflux disease. His medications on entry into the study included nifedipine, simvastatin, acetylsalicylic acid, and omeprazole. Two weeks after his first dose, he was hospitalized with chest pain, and in the emergency room, he was reported to have received sublingual and topical nitroglycerin. His blood pressure was reported to have decreased following nitrate administration and the decreased blood pressure stated was also described as difficult to reverse. According to the hospital notes available, the "NP" (presumably nitropaste) was removed at 04:00 hours and he was still hypotensive at 06:00 hours (BP 76/40). He was moved to a holding area from the emergency room at 08:15 hours. Hospital records obtained indicated that he had had a coronary angiogram 3 or 4 years prior to this episode which was normal. He was also reported to have had a Barrett's esophagus, had had an upper gastrointestinal endoscopy during the screening period for Study LVCR, and was being followed by a gastroenterologist. Subsequent investigations during this hospitalization indicated esophageal spasm as a cause of his chest pain. The patient was discharged and continued in the study and completed participation successfully. The chest pain was assessed as unrelated to study drug. At present, it is unclear whether the hypotensive episode following topical nitrate was augmented by IC351 (last dose of IC351 was administered on the day prior to nitrate administration), because topical nitrate alone (if inadequately removed) may be associated with a hypotensive response.

Medical officer's comment:
This case underscores the need for additional information required for Nitrate and IC 351 interactions. The safety data base in this study is similar to the the other placebo controlled Phase III studies.

9.5.4. Dose Effect on Adverse Events in Controlled studies:
Table 39 reflects the dose related adverse events in the controlled studies (including LVCK)

Table 39 Dose Effect on Adverse Events

TABLE (SOURCE Table H 24 , LVBK, LVCO, LVDJ, LVCK)

Event Classification	Placebo		IC_10mg		IC_20mg	
	n	%	n	%	n	%
HEADACHE	9	3.4	28	8.9	33	10.6
DYSPEPSIA	2	0.8	25	7.9	38	12.2
BACK PAIN	5	1.9	15	4.8	16	5.1
MYALGIA	3	1.1	18	5.7	14	4.5
RHINITIS	8	3.1	11	3.5	9	2.9
VASODILATATION	4	1.5	10	3.2	14	4.5

Medical officer's comment:

1) The most frequent adverse reactions across all phase III studies were; headache, dyspepsia, back pain, myalgia, flushing and nasal congestion.
2) Headache ,dyspepsia and flushing and back pain may have dose related clinical significance,(LVDJ,LVCQ,LVCO) and long term open label studies(LVBL) where some patients discontinued due to above mentioned adverse events corroborate this. This incidence tended to increase with the increase in dose from 10 to 20 mg.

2) This reviewer believes that 10mg has a very similar efficacy , and better safety profile than 20mg.

9.5.5 Safety Information From clinical Pharmacologic Studies.

The reader is also referred to clinical pharmacology section .

9.5.5.1 Safety and Tolerability Evaluations

During the clinical pharmacology program, subjects were studied at a number of clinical research sites. Tolerability and routine safety assessments were performed by recording adverse events and by measuring vital signs, 12-lead electrocardiograms (ECG's), and a battery of laboratory safety tests, as well as by physical examination. 1034 subjects received at least one dose of IC351 in the 42 completed clinical pharmacology studies. This includes the number of subjects dosed within the subgroups studied (healthy subjects and special populations, males and females, single and multiple doses) .

9.5.5.2 Frequent Adverse Events:

1. Headache was reported by 42% of subjects following IC351 and by 26% of subjects following placebo . There were a total of 416 reports of headache for subjects in the IC351-treated group, of which only 4 (0.4%) were rated as severe, compared to 3 (0.6%) severe events out of 142 reports for placebo.

2. Back pain was reported by 26% of subjects following IC351 and by 6% of subjects following placebo. There were a total of 253 reports of back pain for subjects in the IC351-treated group, of which only 9 (0.9%) were rated as severe, compared to 1

(0.2%) severe events out of 34 reports for placebo.
3. Myalgia was reported by 21% of subjects following IC351 and by 6% of subjects following placebo. There were a total of 210 reports of myalgia for subjects in the IC351-treated group, of which only 3 (0.3%) were rated as severe, compared to 0 (0.0%) severe events out of 30 reports for placebo.

4. Cardiovascular adverse events potentially related to a decrease in blood pressure include dizziness, postural hypotension, or syncope. Dizziness is of a diverse etiology, whereas syncope is more often related to reduced blood pressure. The incidence of these adverse events was similar following different doses of IC351 and placebo. These adverse events generally appeared within the first 2 hours after dosing in both placebo- and IC351-treated subjects and were short-lived. When the individual cases of syncope were examined, they occurred either following nitrate administration in the nitrate-interaction studies or appeared to be of a vasovagal etiology and not related to IC351 administration.

-No deaths occurred during the clinical pharmacology program.
-Five serious adverse events occurred in four subjects. Three of the serious adverse events occurred following placebo administration, and one subject experienced two serious adverse events following IC351. (Subject 1019, a 27-year-old healthy Japanese subject with no relevant medical history, experienced a spontaneous left pneumothorax). See Table 40

Table 40: Serious Adverse Events in Clinical Pharmacology Studies

Serious Adverse Events in Clinical Pharmacology Studies:(Source, Table ISS. 5. 5.)

Protocol			Dose		Body System	Event		Relationship	D/C
Treatment: Metoprolol & placebo									
H6D-EW-LVAW	8	49	NA	~13 to 14 days	Body as a whole	Shock	Circulatory collapse after stress	None	Yes
Treatment: Placebo & IMDUR®									
H6D-EW-LVBY	2053	70	NA	3	Cardiovascular system	Angina pectoris	Unstable angina	Improbable	Yes
Treatment: 5 mg IC351 & IMDUR®									
H6D-EW-LVBY	3050	41	5	16	Cardiovascular system	Angina pectoris	Angina	None	No
			5	46	Musculo skeletal system	Bone disorder	Laminectomy	None	No
Treatment: Placebo & 0.6 g/kg alcohol									
H6D-EW-LVDO	31	41	NA	12	Body as a whole	Abdomina syndrome	Abdominal pain Acute appy.	None	Yes

Medical Officers Comments: These events can not be directly attributed to the drug.

9.5.5.3 Discontinuations Due to Adverse Events:

- Overall, a total of 40 (3%) subjects were discontinued during clinical pharmacology studies of which 20 subjects were discontinued due to adverse events.
- Thirty (3%) of the 990 subjects who received IC351 were discontinued, with 13 (1%) being withdrawn due to adverse events. Of these subjects, 3 (0.3%) were discontinued due to myalgia, 2 (0.2%) were discontinued due to back pain, and 2 (0.2%) were discontinued due to headache.
- Of the 545 subjects who received placebo, 10 (2%) subjects were discontinued with 7 (1%) being withdrawn due to adverse events.

Medical Officers Comments:

1. The overall number of T E AE's including the Cardiovascular related events , discontinuations due to adverse events for subjects receiving IC351 and placebo were comparable.
2. No Deaths were reported and there were none of the SAE was directly attributable to IC351.
3. The treatment emergent AE's ,Headache was reported by 42% of subjects , Back pain was reported by 26% of subjects and Myalgia was reported by 21%. These are high when compared with other studies.
4. The reader is also referred to Clinical Pharmacology section (Drug Interactions)

9.5.6 Safety Information From Open-Label, Long-term Studies

Study LVDR was an open-label study designed to evaluate the safety and tolerability of 20 mg IC351 administered "on demand" over a 6-month period, to a large population of subjects with ED. It enrolled patients from the studies LVCQ (Australia) and LVDJ (Canada).
Studies LVBD and LVBL were open-label studies that enrolled patients from prior phase 2 or phase 3 studies and assessed the safety and tolerability of long-term administration of IC351.The sponsor provided safety update in march 2002 with up to the date combined exposures in studies LVBD and LVBL.

884 patients were exposed to at least 20 mg of the market image formulation or its equivalent for 6 months. Of these patients, 855 were exposed to 20 mg of the market image formulation for 6 months. Seven hundred and seventeen (717) patients were exposed to at least 20 mg of the market image formulation or its equivalent for 1 year, and 586 of these patients were exposed to 20 mg of the market image formulation for 1

year. Table 41:

Table 41:Updated Exposure to Study Drug: LVBD and LVBL(Source safety update 3,02)

Dose	≥6 Months	≥1 Year
≥20mg IC351[a]	884	717
20mg Market Image	855	586

a Doses included 20 mg market image formulation, or 25 mg or 50 mg co-precipitate formulation of IC351.

In the open-label, long-term safety studies LVBD and LVBL,

9.5.6.1 Study LVBD:

A total of 203 patients were enrolled in this study. The mean age of patients was 54.2 years, ranging from 24.3 to 72.6 years. Of the 203 patients, 200 patients (98.5%) were Caucasian, 2 patients (1%) were of African descent, and 1 patient (0.5%) was East/Southeast Asian. The patients' mean weight was 81.3 kg, mean Body Mass Index (BMI) was 25.9 kg/m 2 , and mean height was 176.9 cm. Sixty-two patients (30.5%) were smokers, and 158 patients (77.8%) consumed alcohol at a mean of 8.36 units per week.

9.5.6.1.1 PATIENT EXPOSURE TO IC351

Overall, patients were on therapy for a mean of 526 days and took a mean of 231 doses. The mean number of doses taken per week was 2.94. The total number of patient-years of exposure to IC351 in this study was 288.9, of which 241.7 patient-years (83.7%) was to 20 mg dose as the market image formulation, or _____ or higher (25 mg, 50 mg) as the _____ The 20 mg dose as the market image formulation, or _____ (25 mg, 50 mg) as the _____ was taken by *163 patients (80.3%) for ≥6 months* (182 days), and *by 143patients (70.4%) for ≥12 months* (365 days)

9.5.6.1.2 PATIENT DISPOSITION

A total of 203 patients were enrolled in this study. One hundred and sixty-three (80.3%) completed Visit 10 (18 months) and were discontinued by the Sponsor at this visit or at Visit 11 (21 months), due to the Sponsor's decision to reduce the duration of the study.

9.5.6.1.3 DEATHS

NO DEATHS WERE REPORTED IN THIS STUDY

9.5.6.1.4 SERIOUS ADVERSE EVENTS

Nine (4.4%) serious adverse events were reported in this study (Table 42). None of the

serious adverse events were causally related to IC351 administration.

Table 42 : LVBD:SAE(Source, Table LVBD.4.10)

Event Classification	ALL IC 351 (N=203)	
	n	(%)
PATIENTS WITH >= 1 EVENT	9	(4.4)
PATIENTS WITH NO EVENTS	194	(95.6)
ANGINA PECTORIS	2	(1.0)
BLADDER CALCULUS	1	(0.5)
CHOLELITHIASIS	1	(0.5)
KIDNEY CALCULUS	1	(0.5)
MALAISE	1	(0.5)
URINARY RETENTION	1	(0.5)
VASCULAR ANOMALY	1	(0.5)
VISUAL FIELD DEFECT	1	(0.5)

9.5.6.1. 5 DISCONTINUATION DUE TO ADVERSE EVENTS

There were 9 (4.4%) discontinuations due to adverse events. Three patients had serious adverse events and discontinued.

- One patient discontinued due to development of a visual field defect, which was likely caused by embolism associated with cerebrovascular disease or hypercholesterolemia and not related to IC351.

- One patient was discontinued after he developed angina pectoris.

- One patient underwent interventional treatment for a basilar artery aneurysm discovered during investigation of vertigo.

- The other discontinuations due to adverse events included one patient with headache, one patient with myalgia, and one patient with back pain.

- Three patients discontinued due to "unanticipated benefit" as they reported that their erectile dysfunction had improved and they no longer needed treatment.

In summary, 9 (4.4%) patients discontinued due to an adverse event. As 3 of these events were unanticipated benefits, discontinuations due to all other adverse events were 6/203 (3.0%). One patient each (0.5%) discontinued due to study drug-related adverse events of headache, back pain, and myalgia.

9.5.6.1.6 TREATMENT-EMERGENT ADVERSE EVENTS

The most frequently reported adverse events were dyspepsia, headache, back pain, flu syndrome, pain, vasodilatation (flushing), and myalgia. There was one report of presumed asymptomatic hypotension reported as "a decrease in blood pressure to 100

mm Hg," but as this event occurred during a study visit 20 days after the last prior dose of IC351, it was not related to IC351 administration. There were no reports of postural hypotension or syncope. No cases of myocardial infarctions were reported. No cases of priapism were reported. There were no reports of abnormal color vision. Table43:

Table 43:Treatment-Emergent Adverse Events>2 % (Source Table LVBD.4.8.)

	ALLIC
LVBD	(N=203)
Event Classification	n (%)
PATIENTS WITH >= 1 TESS	140 (69.0)
PATIENTS WITH NO TESS	63 (31.0)
DYSPEPSIA	40 (19.7)
HEADACHE	26 (12.8)
BACK PAIN	25 (12.3)
FLU SYNDROME	15 (7.4)
PAIN	9 (4.4)
VASODILATATION	9 (4.4)
MYALGIA	7 (3.4)
UNEXPECTED BENEFIT	7 (3.4)
ASTHENIA	6 (3.0)
CONJUNCTIVITIS	5 (2.5)

9.5.5.7 STUDY LVBL:

Study LVBL was a multi center study conducted in Europe, Canada, Argentina and Mexico to evaluate the safety and tolerability of 18 months of continued "on demand" dosing of IC351. Doses used were 5 mg, 10 mg, and 20 mg of the market-image formulation. All patients started treatment with 10 mg IC351. Dose titration was employed to allow individual patients to find their most satisfactory dose. A formal interim data lock was executed subsequent to the last patient visit date of 1 November 2001. The cut-off date for reports of death was 25 February 2002.

9.5.5.7.1 PATIENT CHARACTERISTICS

The primary population of study patients was men 18 years or older with a history of erectile dysfunction of at least 3 months duration who had participated in a prior phase 2 trial, LVAC, or the phase 3 studies LVBK, LVBO, LVBN, and LVCE.

A total of 1173 patients were enrolled in this study. The mean age of patients was approximately 57.0 years, ranging from 23.4 to 82.8 years. Of the 1173 patients, 1111patients (94.7%) were Caucasian, 24 patients (2.0%) were Hispanic, 19 patients (1.6 %) were of African descent, 12 patients (1.0%) were West Asian, and 4 patients (0.3%) were East/Southeast Asian. The patients' mean weight was 85.2 kg, mean body mass index was 27.96 kg/m 2 , and mean height was 174.58 cm. At baseline, 299 patients (25.5%) were smokers, and 809 patients (69.0%) consumed alcohol at a mean of 4.83 units per week. Of the 1173 patients, 372 (31.7%) had diabetes mellitus, 350

(29.8%) had hypertension, and 16 (1.4%) had coronary artery disorder (LVBL).

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9.5.5.7.2 PATIENT EXPOSURE TO IC351(11/ 2001:SOURCE SAFETY UPDATE 3/02)

Table 44: Patient Exposure to IC351

Dose		Maximum Continuous Duration		
		≥1 day	≥182 days	≥365 days
		n	n	n
Total	≥5 mg	1173	998	878
	≥10 mg	1173	991	870
	20 mg	970	721	574

9.5.5.7.3 PATIENT DISPOSITION

A total of 1173 patients were enrolled in this study. By the date of data cut-off for the interim analysis, 95 patients (8.1%) had completed Visit 8 (18 months) and had been discontinued by the Sponsor due to the decision to terminate the study, while 819 patients (69.8%) were still on-study. Thirty-one patients (2.6%) had discontinued due to adverse events.

9.5.5.7.4 DEATHS

A total of six deaths were reported in this study LVBL.

-Patient 009-0273, a 39 year old man, committed suicide by hanging. This patient had a preexisting history of multiple sclerosis and depression. The investigator concluded that this event was not related to the study drug or any protocol procedure.

-Patient 007-3072, a 56 year old man, was found dead in his sleep. Prior to enrollment into study LVBL, he had had a cardiology consultation to investigate isolated premature ventricular contractions. Results of a subsequent exercise stress test were reported as normal with no clinical or electrocardiographic evidence for myocardial ischemia. The investigator reported the death as "cardiac arrest." An autopsy was performed, and the results are pending.

-Patient 005-0194 was a 79 year old man who was diagnosed with metastatic cholangiocarcinoma after laparotomy for bowel obstruction and jaundice during study LVBL. After the diagnosis of malignancy was made, the patient was discontinued from

the study. Follow-up information received indicated that the patient had died due to metastatic cholangiocarcinoma.

-Patient 419-1302, a 67 year old man, experienced lymphedema of the right leg, and was hospitalized. A diagnosis of prostate cancer and periaortic abdominal and right periiliac lymphadenopathy with compression edema of the right leg was made and the patient was discharged. The study medication was discontinued. The patient was hospitalized subsequently with acute abdominal pain caused by metastatic prostate cancer. Approximately two months later, the patient died probably as a result of metastatic prostate cancer. The investigator assessed the death as unrelated to study drug (CRF.Patient 419-1302).

-Patient 105-2107, a 71 year old man with diabetes mellitus and hypertension, experiencedcardiac arrest while dancing. The patient was resuscitated, hospitalized, and found to have had a myocardial infarction diagnosed by electrocardiography and elevation of serum creatine kinase. The patient required mechanical ventilation for 15 days, and contracted aspiration pneumonia. Approximately two weeks later, the patient experienced another cardiac arrest and died. The investigator assessed this event as unrelated to study drug (CRF.Patient 105-2107).

-Patient 003-4065 was a 68 year old Caucasian man who had a cardiac arrest . This patient had a prior history of coronary artery disease, myocardial infarction, and hypercholesterolemia. His concomitant medications included aspirin, ramipril, lorazepam, quinine for cramps, and terazosin for nocturia. He received his first dose of IC351 (10 mg) in Study LVBL on 1 August 2000. The dose was increased to 20 mg on 30 August 2000. The last known and recorded dose of study drug was 4 August 2001, however, the patient's study medications and diary were discarded by the patient's wife and hence the exact time and date of last dose prior to the event is unknown. He then collapsed and turned blue. He was taken to a hospital where he was pronounced dead on arrival. The autopsy showed moderate atherosclerosis in the aorta and large vessels with complicated plaque in the abdominal segment. There was coronary atherosclerosis with focal narrowing of the lumen by 80% in the left and 60% in the right coronary arteries, and a small recent hemorrhage into a plaque in the proximal left branch. The cause of death was reported as being due to ischemic heart disease with probable arrhythmia; transmural remote infarct and tri-vessel coronary artery stenosis.

Medical Officers Comments;
None of these deaths could be directly attributed to the drug.

9.5.5.7.5 TREATMENT-EMERGENT ADVERSE EVENTS

The most frequently (5%) reported treatment-emergent adverse events in IC351-treated patients included headache (15.3%), dyspepsia (11.0%), infection (10.1%), back pain (7.3%), nasal congestion (rhinitis, 6.5%), flu syndrome (6.2%), pain (6.1%), and surgical

procedure (6.0%). Other adverse events reported are vasodilatation (flushing), and myalgia. One patient reported that he had abnormal blue vision.

No cases of priapism were reported. There were no instances of hypotension or postural hypotension reported. There was one patient who reported syncope .Table 45

Table 45: LVBL:Treatment-Emergent Adverse Event by Decreasing Frequency to ≥2% in IC351-Treated

Event Classification	IC351 (N = 1173)	
	N	%
Patients with ≥1 TEAE	786	67.0
Patients with no TEAE	387	33.0
Headache	180	15.3
Dyspepsia	129	11.0
Infection	119	10.1
Back pain	86	7.3
Rhinitis	76	6.5
Flu syndrome	73	6.2
Pain	72	6.1
Surgical procedure	70	6.0
Vasodilatation	46	3.9
Myalgia	44	3.8
Abdominal pain	43	3.7

9.5.5.7.5 SERIOUS ADVERSE EVENTS:

Eighty-six patients (7.3%) experienced serious adverse events in this study since its start. Five serious adverse events were assessed by the investigator as related to IC351. Table46

Table 46: LVBL, Summary of Serious Adverse Events by Decreasing Frequency

Event Classification	Total (N = 1173)	
	n	%
Patients with ≥1 SAE	86	7.3
Patients with no SAE	1087	92.7
Myocardial infarct	9	0.8
Accidental injury	6	0.5
Cerebro vascular accident	4	0.3
Cholecystitis	4	0.3
Gastrointestinal carcinoma	4	0.3
Angina pectoris	3	0.3
Atrial fibrillation	3	0.3
Back pain	3	0.3
Heart arrest	3	0.3
Hernia	3	0.3
Infection	3	0.3
Pancreatitis	3	0.3
Pneumonia	3	0.3
Carcinoma	2	0.2
Chest pain	2	0.2
Hyperglycemia	2	0.2
Skin ulcer	2	0.2
Abscess	1	0.1
Adenoma	1	0.1
Arthralgia	1	0.1
Atrial flutter	1	0.1
Carcinoma of lung	1	0.1
Cellulitis	1	0.1
Cerebral infarct	1	0.1
Cholelithiasis	1	0.1
Cyst	1	0.1
Deafness	1	0.1
Death	1	0.1
Deep thrombophlebitis	1	0.1
Depression	1	0.1
Diabetic acidosis	1	0.1
Diabetic coma	1	0.1
Dyspnea	1	0.1
Encephalitis	1	0.1
Esophagitis	1	0.1
Fever	1	0.1
Gastritis	1	0.1
Heart failure	1	0.1
Hematemesis	1	0.1

Patient 005-0201 in study LVBL was a 53 year old man who stated that while driving on the highway, he became nauseous, had blurred vision, felt weak, and fainted. He had

been on study drug for approximately 8 months and his last dose was about 28 hours prior to the event. The patient recovered consciousness when the ambulance personnel arrived. Subsequent investigations revealed no injury and a cardiologic and neurologic evaluation were unrevealing. The investigator assessed the event as "loss of consciousness" (syncope) and possibly related to study drug. The last dose prior to the event was more than 24 hours. The patient's history was more compatible with other causes, such as a transient ischemic attack, a seizure, or the patient's falling asleep at the wheel, and therefore the Sponsor assessed the event as unrelated to study drug.

Patient 007-0236 was a 65 year old man with a history of diabetes mellitus, hypertension, hypercholesterolemia, obesity, a past smoking history, and a family history of coronary artery disease (mother and father had myocardial infarctions). Four days after the last dose of study drug, the patient developed weakness, dyspnea, nausea, and chest pain. He was hospitalized and diagnosed to have had a myocardial infarction. He recovered and was discharged. The investigator assessed the event as possibly related to study drug. As the patient had several risk factors for coronary artery disease and as the last dose of study drug was taken 4 days prior to the event, the Sponsor assessed the event as unrelated to study drug.

Patient 405-1064 was a 73 year old man with a past history of diabetes mellitus and hypertension. This patient had several hypoglycemic reactions while participating in the study. He had also had some episodes of chest pain. During the management of one of the hypoglycemic episodes, a myocardial infarction was diagnosed on the basis of electrocardiography and abnormal cardiac enzymes. A stress test done later revealed silent ischemia. The investigator assessed the event as related to study drug. As the patient had underlying coronary risk factors and as silent myocardial infarctions are known to occur in patients with diabetes mellitus, the Sponsor assessed the event as unrelated to study drug.

Patient 005-4118 was a 49 year old man who had a history of hypertension, coronary artery disease, hypothyroidism, and had been taking aspirin for coronary artery disease prevention, developed gastroesophageal reflux. Five weeks later, he developed acute mid-abdominal pain, nausea, and vomited "coffee ground" secretions, and was hospitalized. Upper gastrointestinal endoscopy with biopsy revealed esophagitis and superficial chronic gastritis, and Helicobacter pylori. The patient was treated with omeprazole and discharged from the hospital with a final diagnosis of esophagitis, mild chronic gastritis, and H. pylori infection. The patient experienced nausea with subsequent dosing with study drug and discontinued from the study. The Sponsor assessed the event as unrelated to study drug as the patient's history and biopsy findings suggested that the likely cause was chronic aspirin-induced gastritis.
There were 9 cases of myocardial infarction. In all these instances, the patient had underlying conditions that were risk factors for coronary artery disease. None of these events are felt to be causally related to study drug, even though the investigator had assessed the events to be related to study drug in 2 instances.

9.5.5.7.7 DISCONTINUATION DUE TO ADVERSE EVENTS

There were a total of 63 (5.4%) discontinuations due to adverse events. Discontinuation rates for any individual adverse event (eg, headache) were less than 1%.In addition, one patient (407-1078) discontinued due to a pre existing condition of gastric spasm. 23 patients (1.9 %) discontinued due to a serious adverse event. The remaining non serious adverse events recorded as a reason for discontinuation included headache, dyspepsia, and back pain.

Vital Signs

No clinically significant changes occurred in vital signs that were attributable to IC351 administration.

Clinical Laboratory Evaluation and ECG

There were no clinically significant laboratory abnormalities attributable to IC351. During the study, three patients experienced liver enzyme elevations. There were no reports of neutropenia or thrombocytopenia attributable to IC351. No clinically significant changes in ECG values were observed.

Medical Officers Comments:

These open label studies showed a higher incidence of frequent adverse events when compared to placebo controlled trials. Some patients discontinued because of 20 mg related events. Six deaths were reported however these could not be directly attributed to the drug. The serious adverse events were comparable to the controlled trials and attribution to the drug could not be made.

9.5.5.8 STUDY LVDR

Study LVDR was an open-label study designed to evaluate the safety and tolerability of 20 mg IC351 administered "on demand" over a 6-month period, to a large population of subjects with ED. Patients who completed Study LVCQ or LVDJ were eligible to participate in this study. A total of 331 patients participated in the study. The patient characteristics and demographic features were similar to the other long term studies.

9.5.5.8.1 TREATMENT-EMERGENT ADVERSE EVENTS

There were 187 (56.5%) patients with TE AE's. The most frequently (5%) reported treatment-emergent adverse events in IC351-treated patients included headache (11.8%), dyspepsia (10.6%), nasal congestion (rhinitis,7.33%), and vasodilatation (flushing, 5.1%). Table 47.

Table 47; Treatment-Emergent Adverse Events>2%