COMPOSITION
Each tablet contains 10 mg or 20 mg tadalafil.

CLINICAL PARTICULARS
1. Therapeutic indications
Treatment of erectile dysfunction.
In order for **link36** to be effective, sexual stimulation is required.
link36 is not indicated for use by women.

2. Posology and method of administration
For oral use
Use in adult men
The recommended dose is 10 mg taken prior to anticipated sexual activity and without regard to food. In those patients in whom tadalafil 10 mg dose not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.
The maximum dosing frequency is once per day.
Tadalafil 10 and 20 mg is intended for use prior to anticipate sexual activity and is not recommended for continuous daily use.
Use in elderly men
Dosage adjustments are not required in elderly patients.
Use in men with impaired renal function
Dosage adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose. (See Pharmacokinetics properties).
Use in men with impaired hepatic function
The recommended dose of Tadalafil is 10 mg taken prior to anticipated sexual activity and without regard to food. There is limited clinical data on the safety of Tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. (See Special warnings and special precautions for use and Pharmacokinetics properties).
Use in men with diabetes
Dosage adjustments are not required in diabetic patients.
Use in children and adolescents
Tadalafil should not be used in individuals below 18 years of age.

3. Contraindications
In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated. (See section Interaction with other medicinal products and other forms of interaction).
Agents for the treatment of erectile dysfunction, including Tadalafil, should not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.
The following groups of patients with cardiovascular disease were not included in clinical trails and the use of tadalafil is therefore contraindicated:
• 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 within the last 6 months,
Tadalafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.
Tadalafil should not be used in patients with hypersensitivity to tadalafil.

4. Special warnings and Special precautions for use
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.
Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section Pharmacodynamic properties) and as such potentiate the hypotensive effect of nitrates (See section Contraindications). Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either postmarketing and/or in clinical trails. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to Tadalafil, to sexual activity, or to a combination of these or other factors.
Visual defects and causes of non-arteritic anterior ischemic optic neuropathy have been reported in connection with the intake of Tadalafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking Tadalafil and consult a physician immediately.
There is limited clinical data on the safety of Tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.
Agents for the treatment of erectile dysfunction, including Tadalafil should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).
The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment.
It is not known if Tadalafil is effective in patients with spinal cord injuries and patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.
Tadalafil should not be administered to patients with hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose –galactose malabsorption.
In patients who are taking alpha (1) blockers, such as doxazosin, concomitant administration of Tadalafil may lead to symptomatic hypotension in some patients (see Interaction with other medicinal products and other forms of interaction). Therefore, the combination of tadalafil and alpha blockers is not recommended.
Caution should be exercised when prescribing Tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has b een observed if the drugs are combined (see Interaction with other medicinal products and other forms of interaction).
The safety and efficacy of combination of Tadalafil and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

5. Interaction with other medicinal products and other forms of interaction
Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.
Effects of other medicinal products on tadalafil
Tadalafil is principally metabolized by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily) increased tadalafil (10-mg) exposure (AUC) 2-fold and Cmax by 15%, relative to the AUC and Cmax values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20-mg) exposure (AUC) 4-fold and Cmax by 22%. Ritonavir, a protease inhibitor (200 mg dose given twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20-mg) exposure (AUC) 2-fold with no change in Cmax. Although specific interactions have not been studies, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil. Consequently the incidence of the undesirable effects might be increased.
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. There is thus the potential of drug interactions mediated by inhibition of transporters.
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88%, relative to the AUC values for tadalafil alone (10 mg dose). It can be expected that concomitant administration of other CYP3A4 inducers such as Phenobarbital, phenytoin and carbamazepine, will also decrease plasma concentrations of tadalafil.
Effects of tadalafil on other medicinal products
In clinical studies, tadalafil (10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated (See section Contraindications). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose.
Thus, in a patient prescribed Tadalafil, where nitrate administration is deemed medically necessary a life-threatening situation, at least 48 hours should have elapsed after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administrated under close medical supervision with appropriate haemodynamic monitoring.
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by CYP450 isoforms. Studies have confirmed that tadalafil dose not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9, and CYP2C19.
Tadalafil (10and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin. (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin. Tadalafil (10 and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid. In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive agents was examined. Major classes of antihypertensive agents were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide) and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta blockers , and/or alpha blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studies in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood –pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects.
In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medications tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers –see below) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trail data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medications. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medications.
In subjects receiving concomitant tadalafil (20 mg) and doxazosin (8 mg daily), an alpha (1)-adrenergic receptor blocker, there was an augmentation of the blood-pressure lowering effect of doxazosin. This effect was still present at 12 hours postdose and had generally disappeared at 24 hours. The number of subjects with potentially clinically significant standing- blood- pressure decreases was greater for the combination. Some subjects experienced dizziness but no cases of syncope were reported. Lower doses of doxazosin have not been studied. Therefore, the combination of tadalafil and alpha blockers is not recommended. In a single study in 18 healthy volunteers, tadalafil (10 and 20 mg) had no clinically significant effect on blood pressure changes due to tamsulosin, a selective alpha (1A)-adrenergic receptor blocking agent. It is not known how this extrapolates to other alpha (1A)-adrenergic receptor blocking agents.
Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by co-administration with tadalafil (10 or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximize the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml or 40% alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medications.
Specific interaction studies with antidiabetic agents were not conducted.

6. Pregnancy and lactation
Tadalafil is not indicated for use by women. There are no studies of tadalafil in pregnant women.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day.

7. Effects on ability to drive and use machines
Tadalafil is expected to have no or negligible influence on the ability to drive and use machines. No specific studies have been performed to evaluate a potential effect. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trails was similar, patients should be aware of how they react to Tadalafil, before driving or operating machinery.

8. Undesirable effects

Table 1: Very common adverse reactions (>1/10)

System Organ Class	Adverse reaction	TADALAFIL 10-20 mg (%) N=724	Placebo (%) N=379
Nervous System	Headache	14.5	5.5
Gastrointestinal	Dyspepsia	12.3	1.8

Table 2: Common adverse reactions (>1/100,<1/10)

System Organ Class	Adverse reaction	TADALAFIL 10-20 mg (%) N=724	Placebo (%) N=379
Nervous System	Dizziness	2.3	1.8
Vascular	Flushing	4.1	1.6
Respiratory, thoracic and mediastinal	Nasal Congestion	4.3	3.2
Musculoskeletal and Connective tissue	Back pain Myalgia	6.5 5.7	4.2 1.8

Swelling of eyelids, sensations described as eye pain and conjunctival hyperaemia are uncommon adverse reactions.
The adverse events reported with tadalafil were transient, and generally mild or moderate.
Adverse event data are limited in patients over 75 years of age.

9. Overdose
Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

PHARMACOLOGICAL PROPERTIES
1. Pharmacodynamic properties
Pharmacotherapeutic group: drugs used in erectile dysfunction (ATC Code G04B E)
Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.
Studies in vitro have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is >10,000-fold more potent for PDE5 than for PDE1,PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.
Three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness to Tadalafil.
Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.
Tadalafil administrated to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.
In a study to assess the effects of tadalafil on vision, no impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in color vision were rare (<0.1%).
Three studies were conducted in men to assess the potential effect on spermatogenesis of Tadalafil 10mg (one 6- month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.
Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe) , etiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81% of patients reported that Tadalafil improved their erections as compared to 35 % with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking Tadalafil (86%, 83%, and 72% for mild, moderate, and severe, respectively, as compared to 45%, 42%, and 19% with placebo). In the primary efficacy studies, 75% of intercourse attempts were successful in Tadalafil treated patients as compared to 32% with placebo.

2. Pharmacokinetic properties
Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, thus Tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 L, indicating that tadalafil is distributed into tissue. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.
Biotransformation
Tadalafil is predominantly metabolized by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the menthylcatechol glucuronide. This metabolite is at least 13.000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.
Elimination
The mean oral clearance for tadalafil is 2.5 L/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).
Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.
Pharmacokinetic determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special Population
Elderly
Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and doses not warrant a dose adjustment.
Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5-20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, Cmax was 41% higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.
Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of Tadalafil in patients with severe hepatic insufficiency (child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.
Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19% lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

IN ACTIVE INGREDIENTS
Lactose, Microcrystalline cellulose, Hydroxypropyl cellulose, Croscarmellose sodium, Sodium lauryl Sulphate, Yellow iron oxide, Colloidal silicon dioxide& Magnesium stearate.

PRESENTATION
link36 20 mg film-coated tablets: 4 tablets
link36 10 mg film-coated tablets: 4 tablets
link36 20 mg film-coated tablets: 1 tablets
link36 10 mg film-coated tablets: 1 tablets

STORAGE CONDITIONS
Store below 30°C.