SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEGRA 50 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains
Active substance:
Sildenafil 50.0 mg (sildenafil citrate of equivalent quantity)

Excipients:
Croscarmellose sodium 15.0 mg
Lactose monohydrate 4.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablet
Blue film-coated hexagonal tablets marked “50” on one side and “DGR” on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
DEGRA is indicated for symptomatic treatment of erectile dysfunction, described as inability to achieve and maintain a penile erection sufficient for satisfactory sexual performance.
In order for DEGRA to be effective, sexual stimulation is required.
DEGRA is not indicated in women.

4.2. Posology and method of administration

Posology
The recommended dose for most patients in symptomatic treatment of erectile dysfunction, described as inability to achieve and maintain a penile erection sufficient for satisfactory sexual performance is 50 mg taken as needed approximately one hour before sexual activity.

Frequency and duration of administration:
Based on efficacy and tolerability, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day.

Method of administration
DEGRA Tablets are for oral use.

If it is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).
Concomitant use of potent cytochrome P450 CYP3A4 inhibitors (e.g. erythromycin, saquinavir, ketoconazole, itraconazole) has been associated with increased plasma concentrations of sildenafil

(see section 4.5). Since higher plasma concentrations may increase both the efficacy and adverse events, a starting dose of 25 mg should be considered in these patients.

Co-administration of sildenafil with ritonavir is not advised (see section 4.5)

DEGRA was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated (see section 4.3).

When DEGRA is concomitantly used with alpha-blockers, in order to minimize the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see section 4.4 and 4.5).

Additional information on special populations

Renal/hepatic impairment:
In patients with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min) (see section 5.2 Renal Impairment), dosage adjustments are not required. Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) (see section 5.2 Hepatic Impairment) a 25 mg dose should be considered.

Pediatric population:
Sildenafil is not indicated for children (below 18 years of age).

Geriatric population:
Dosage adjustment is not required in elderly patients.

4.3. Contraindications

- It is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates and its co-administration with nitric oxide donors (such as amyl nitrite, butyl nitrite) or nitrates in any form (nitroglycerine, isosorbide mononitrate, isosorbide nitrate, pentaerythritol tetranitrate, erythritol tetranitrate, isosorbide dinitrate/ phenobarbital) is therefore contraindicated.
- The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).
- It is contraindicated in patients with non-arteritic anterior ischemic optic neuropathy.
- Drugs used for erectile dysfunction (including sildenafil) are not recommended for patients for whom sexual activity is inadvisable (cardiovascular disorders such as unstable angina or severe cardiac failure).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available:

- Severe hepatic impairment,
- Hypotension (blood pressure <90/50 mmHg),
- Recent history of stroke or myocardial infarction,
- Known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4.4. Special warning and precautions for use

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is initiated.

Cardiovascular risk factors

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. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

DEGRA potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Priapism

Agents for the treatment of erectile dysfunction, including sildenafil, 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 anemia, multiple myeloma or leukemia).
Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension treatments containing sildenafil, or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Effects on vision

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil

and other PDE5 inhibitors (see section 4.8). Cases of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). Patients should be advised that in case of sudden visual defect, they should stop taking DEGRA and consult a physician immediately (see section 4.3).

Concomitant use with ritonavir
Co-administration of sildenafil with ritonavir is not advised (see section 4.5).

Concomitant use with alpha-blockers
Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5). This is most likely to occur within 4 hours post sildenafil dosing. In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

Effect on bleeding
Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of DEGRA to patients with bleeding disorders or active peptic ulceration. Therefore DEGRA should be administered to these patients only after careful benefit-risk assessment.

The risk of retinal vein occlusion is especially increased in elderly patients with increased blood viscosity.

Women
DEGRA is not indicated for use by women.

The film coating of DEGRA tablet contains lactose. DEGRA should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet; i.e. essentially sodium-free".

4.5. Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on DEGRA:
In vitro studies:
Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies:
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors such as ketoconazole, erythromycin, cimetidine. Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a dose of 25 mg should be

considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with single dose sildenafil (100 mg) resulted in a 4-fold (300%) increase in sildenafil C_{max} and an 11-fold (1,000%) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil has no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see section 4.2).

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with single-dose sildenafil 100 mg resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics (see section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin administered as 500 mg daily for 3 days on C_{max}, T_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite.

Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with 50 mg sildenafil to healthy volunteers.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of sildenafil.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme (ADE) inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).
In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and C_{max}, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a serious interaction with sildenafil.

Effects of DEGRA on other medicinal products

In vitro studies:

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50}>150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, DEGRA is not expected to alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:

Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates. Its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated (see section 4.3).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see section 4.2 and 4.4). In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

No significant interactions were shown when 50 mg sildenafil was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by 150 mg aspirin.

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum alcohol levels of 80 mg/dl.

Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers (see section 5.1).

Sildenafil (100 mg) does not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

In healthy male volunteers, sildenafil at steady state (80 mg t.i.d.) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg b.i.d.).

4.6. Fertility, pregnancy and lactation

General principles:
Pregnancy category is: B
DEGRA is not indicated for use by women.

Women of child-bearing potential/Contraception
DEGRA is not indicated for use by women.

Pregnancy
No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil (see section 5.3).
There are no adequate data for use in pregnant women.

Fertility
There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males (a dose producing an AUC value of more than 25 times the human male AUC).
There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

4.7. Effects on ability to drive and use machinery
No studies on the effects on the ability to drive and use machines have been performed.
As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be careful when driving and operating machinery.

4.8. Undesirable effects
The safety profile of DEGRA is based on 9570 patients in 74 double-blind placebo-controlled clinical studies. The most commonly reported adverse reactions among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and vision blurred.
Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >10 years. Because not all adverse reactions are reported to the Marketing Authorization Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

Listed below are aall medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to ≤1/10), uncommon (≥1/1,000 to ≤1/100), rare (≥1/10,000 to, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated based on available data).
The frequency of medically important adverse reactions reported from post-marketing experience is included as not known.

Infections and infestations
Uncommon : Rhinitis

Immune system disorders
Uncommon : Hypersensitivity reactions

Nervous system disorders
Very common : Headache
Common : Dizziness
Uncommon : Somnolence, hypoesthesia
Rare : Cerebrovascular accident, transient ischemic attack, seizure*, seizure recurrence* syncope

Eye disorders
Common : Visual color distortion **, visual disorders, vision blurred
Uncommon : Lacrimation disorders***, eye pain, photophobia, photopsia, ocular hyperaemia, visual brightness, conjunctivitis
Rare : Non-arteritic anterior ischemic optic neuropathy (NAION)*, retinal vascular occlusion*, retinal hemorrhage, arteriosclerotic retinopathy, retinal disorder, glaucoma, visual field defect, diplopia, visual acuity reduced, myopia, asthenopia, vitreous floaters, iris disorder, mydriasis, *halo* vision, eye edema, eye swelling, eye disorder, conjunctival hyperemia, eye irritation, abnormal sensation in eye, eyelid edema, scleral discoloration

Ear and labyrinth disorders
Uncommon : Vertigo, tinnitus
Rare : Deafness

Cardiac disorders
Uncommon : Tachycardia, palpitations
Rare : Sudden cardiac death*, myocardial infarction, ventricular arrhythmia*, atrial fibrillation, unstable angina

Vascular disorders
Common : Flushing, hot flush
Uncommon : Hypertension, hypotension

Respiratory, thoracic and mediastinal disorders
Common : Nasal congestion
Uncommon : Epistaxis, sinus congestion
Rare : Throat tightness, nasal edema, nasal dryness

Gastrointestinal disorders
Common : Nausea, dyspepsia
Uncommon : Gastro esophageal reflux, vomiting, abdominal pain upper, dry mouth
Rare : Hypoesthesia oral

Skin and subcutaneous tissue disorders
Uncommon : Rash
Rare : Steven Johnson Syndrome*, toxic epidermal necrolysis*

Musculoskeletal, connective tissue and bone disorders
Uncommon : Myalgia, pain in extremity

Renal and urinary disorders
Uncommon : Hematuria

Reproductive system disorders
Rare : Penile hemorrhage, priapism*, hematospermia, erection increased

General disorders and administration site conditions
Uncommon : Chest pain, fatigue, feeling hot
Rare : Nervousness

Investigations
Uncommon: Heart rate increased

* Reported during post-marketing surveillance only
**Visual color distortions : Chloropsia, chromatopsia, cyanopsia, erythropsia and xanthopsia
***Lacrimation disorders : Dry eye, lacrimal disorder and lacrimation increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Cenre (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose
In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.
Treatment:
In cases of overdose, standard supportive measures should be adopted as required. Dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in erectile dysfunction; Phosphodiesterase Inhibitors
ATC Code: G04B E03

Sildenafil is an oral therapy for erectile dysfunction. In a natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant

effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for DEGRA to produce its intended beneficial pharmacological effects.

Pharmacodynamic effects
Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Clinical efficacy and safety
Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

In a study of the hemodynamic effects of a single oral 100 mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (>70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 7% and 6% respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9%. Sildenafil showed no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries.

A double-blind, placebo-controlled exercise stress trial evaluated 144 patients with erectile dysfunction and stable angina who regularly received anti-anginal medicinal products (except nitrates). The results demonstrated no clinically relevant differences between sildenafil and placebo in time to limiting angina.

Mild and transient differences in color discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in color discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. DEGRA has no effect on visual acuity or contrast sensitivity. In a placebo-controlled cross-over study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100 mg) was well-tolerated and visual tests conducted demonstrated no clinically significant changes (visual acuity, Amsler grid, color discrimination, simulated traffic light, Humphrey perimeter and photostress).

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 4.6).

Further information on clinical trials
In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischemic heart disease (5.8%), hyperlipidemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% with 25 mg, 74% with 50 mg and 82% with 100 mg compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo. Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischemic heart disease (69%), hypertension (68%), transurethral resection of the prostate (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long term studies.

5.2. Pharmacokinetic properties

General properties
Absorption
Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25 mg-100 mg).

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Distribution
The mean steady state volume of distribution for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Biotransformation
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this

metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolized, with a terminal half-life of approximately 4 h.

Elimination
The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

Linearity/Non-linearity
The pharmacokinetics of DEGRA is dose proportional over the recommended dose range.

Pharmacokinetics in special patient groups
Elderly
Healthy elderly volunteers aged 65 years or over had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and C_{max} of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant.
In volunteers with severe renal impairment (creatinine clearance <30 ml/min), sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 79% and 200% respectively.

Hepatic insufficiency
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increase in AUC (84%) and in C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function has not been studied.

5.3. Preclinical safety data
Non-clinical data revealed no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Microcrystalline cellulose
Calcium hydrogen phosphate, anhydrous
Croscarmellose sodium
Magnesium stearate
Indigo carmine (E132)

Hydroxypropyl methylcellulose
Lactose monohydrate
Titanium dioxide (E171)
Triacetin
Iron oxide yellow (E172)

6.2. Incompatibilities
None known.

6.3. Shelf life
48 Months

6.4. Special precautions for storage
Store at room temperature below 30°C.
Keep out of the reach and sight of children.

6.5. Nature and contents of container
PVC/Al foil blister packaging in box.
1, 4 or 8 film coated tablets.

6.6. Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
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8. MARKETING AUTHORIZATION NUMBER

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9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 06.01.2005
Date of last renewal :

10. DATE OF REVISION OF TEXT

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