1.0 NAME OF THE MEDICINAL PRODUCT

1.1 Brand Name: AKUSIL D

1.2 Generic Name: Sildenafil & Dapoxetine Tablets

1.3 Strength: 100 mg + 60 mg

1.4 Pharmaceutical Form: Tablets

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains:
Sildenafil Citrate USP
Eq. to Sildenafil 100 mg
Dapoxetine Hydrochloride
Eq. to Dapoxetine 60 mg
Colours: Indigo Carmine, Brilliant Blue FCF Lake & Titanium Dioxide BP

For a full list of excipients, see section 6.1

3.0 PHARMACEUTICAL FORM & DESCRIPTION

Film Coated Tablet
Blue coloured, diamond shaped, biconvex, "100" engraved on one side plain on other side & film coated tablets.

4.0 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Commonly the Sildenafil 100mg + Dapoxetine 60mg Tablets are prescribed for male erectile dysfunction, and premature ejaculation.
Sildenafil 100mg + Dapoxetine 60mg Tablets should only be prescribed to patients that meet all the following criteria:
a) Dapoxetine
· An intravaginal ejaculatory latency time (IELT) of less than two minutes; and
· Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and
· Marked personal distress or interpersonal difficulty as a consequence of PE;
· Poor control over ejaculation; and
·A history of premature ejaculation in the majority of intercourse attempts over the prior 6 months.
b) Sildenafil
Inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
Note: In order for Sildenafil to be effective, sexual stimulation is required". Superwelgra, a Sildenafil - Dapoxetine combination tablet is used to achieve and maintain erections and delay premature ejaculation in men resulting in enhanced sexual pleasures.

4.2 DOSAGE AND ADMINISTRATION

The recommended dose for Sildenafil is 50mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg.

The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

Special populations

Elderly

Dosage adjustments are not required in elderly patients (≥ 65 years old).

Renal impairment

The dosing recommendations described in "Use in adults" apply to patients with mild to moderate renal impairment (creatinine clearance= 30-80 mL/min).

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.

Hepatic impairment

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) 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.

Paediatric population

Sildenafil is not indicated for individuals below 18 years of age.

4.3 CONTRAINDICATIONS

Contraindicated in patients with a known hypersensitivity to the active substance or to any of the Excipients.

Hypersensitivity to the active substance or to any of the excipients. Significant pathological cardiac conditions such as:

Heart failure (NYHA class II-IV)

Conduction abnormalities such as AV block or sick sinus syndrome

Significant ischemic heart disease

Significant valvular disease.

A history of syncope.

A history of mania or severe depression.

Concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after Dapoxetine has been discontinued. Concomitant treatment with thioridazine, or within 14 days of discontinuing treatment with thioridazine. Similarly, thioridazine should not be administered within 7 days after Dapoxetine has been discontinued.

Concomitant treatment with serotonin reuptake inhibitors [selective serotonin reuptake inhibitors

(SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)] or other medicinal/herbal products with serotonergic effects [e.g., L-tryptophan, triptans, tramadol, linezolid, lithium, St. John's Wort (Hypericum perforatum)] or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after Dapoxetine has been discontinued Concomitant treatment of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazadone, nelfinavir, atazanavir, etc. Moderate and severe hepatic impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Sildenafil citrate should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. Physicians should carefully consider whether their patients with under-lying cardiovascular disease could be affected adversely by such dilatory effects, especially in combination with sexual activity.

Caution is advised when Phosphodiesterase Type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including sildenafil citrate, and alpha-adrenaline blocking agents are both dilators with blood pressure lowering effects. When dilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly wading to symptomatic hypo tension. Sildenafil citrate has systemic dilatory properties and may augment the blood pressure lowering effect of other anti-hypertensive medications. Sildenafil citrate should be used with caution in patients with anatomical deformation of the penis (such as strangulation, cavernous fibrosis or Clapeyron's disease), or in patients who have conditions which may predispose them to priapic (such as sickle cell anaemia, multiple myeloma, or leukaemia). The safety and efficacy of combinations of sildenafil citrate with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.
Ethanol Combining alcohol with Dapoxetine may increase alcohol-related precognitive effects and may also enhance electrocardiogram adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking Dapoxetine.

Syncope Dapoxetine should be prescribed with caution in patients taking medicinal products with dilatation properties (such as alpha adrenaline receptor antagonists, nitrates, PDE5 inhibitors) due to possible reduced thermostatic tolerance.

Moderate CYP3A4 inhibitors
Caution is advised in patients taking moderate CYP3A4 inhibitors and the dose is restricted to 30 mg.

Potent CYP2D6 inhibitors

Caution is advised if increasing the dose to 60 mg in patients taking potent CYP2D6 inhibitors or if increasing the dose to 60 mg in patients known to be of CYP2D6 poor metabolize genotype, as this may increase exposure levels, which may result in a higher incidence and severity of dose dependent adverse events.

Suicide/suicidal thoughts

Antidepressants, including SSRIs, increased the risk compared to placebo of suicidal thinking and suicidality in short-term studies in children and adolescents with Major Depressive Disorder and other psychiatric disorders.

Mania

Dapoxetine should not be used in patients with a history of mania/hypo mania or bipolar disorder and should be discontinued in any patient who develops symptoms of these disorders. Seizure: Due to the potential of SSRIs to lower the seizure threshold, Dapoxetine should be discontinued in any patient who develops seizures and avoided in patients with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored. Use in children and adolescents under age 18: Dapoxetine should not be used in individuals below 18 years of age.

Co-morbid depression and psychiatric disorders

Men with underlying signs and symptoms of depression should be evaluated prior to treatment with Dapoxetine to rule out undiagnosed depressive disorders. Concomitant treatment of Dapoxetine with antidepressants, including SSRIs and Saris, is contraindicated. Physicians should encourage patients to report any dis-tressing thoughts or feelings at any time and if signs and symptoms of depression develop during treatment, Dapoxetine should be discontinued.

Renal impairment

Dapoxetine is not recommended for use in patients with severe renal impairment and caution is advised in patients with mild or moderate renal impairment.

Lactose intolerance

Patients with rare hereditary problems of galactic intolerance, the Lapp lactate deficiency or glucose galactic absorption should not take this medicine.

CYP3A4 inhibitors

CYP3A4 inhibitors, such as ketoconazole, itraconazole, peritoneal, sanguinary, streptomycin, nefarious, Scandinavia and atavistic, is contraindicated.

Moderate CYP3A4 inhibitors

Caution is advised if Dapoxetine in 60 mg doses is taken concomitantly with a moderate CYP3A4 inhibitor.

PDE5 inhibitors

Dapoxetine should be prescribed with caution in patients who use PDE5 inhibitors due to possible reduced thermostatic tolerance.

Tuberculosis

Dapoxetine should be prescribed with caution in patients who use alpha adrenaline receptor antagonists due to possible reduced thermostatic tolerance.

Warfarin

There are no data evaluating the effect of chronic use of warfarin with Dapoxetine; therefore, caution is advised when Dapoxetine is used in patients taking warfarin chronically.

4.5 DRUG INTERACTIONS

Nitrates

Concomitant use of sildenafil citrate with nitrates in any form is contraindicated

Peritoneal and other Potent CYP3A Inhibitors

Concomitant use of Sildenafil citrate with peritoneal and other potent CYP3A inhibitors is not recommended.

Alpha-blockers

Use caution when co-administering alpha-blockers with sildenafil citrate because of additive blood pressure-lowering effects.

Amlodipine

When sildenafil 100 mg oral was co-administered with amphetamine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

Potential for interaction with monoamine oxidase inhibitors

Dapoxetine should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after Dapoxetine has been discontinued.

Potential for interaction with thioridazine

Thioridazine should not be administered within 14 days after dapoxetine has been discontinued.

Medicinal / herbal products with serotonergic effects

Dapoxetine should not be used concomitantly with other SSRIs, MAOIs, and other medicinal/herbal products or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after Dapoxetine has been discontinued.

CNS active medicinal products: caution is advised if the concomitant administration of Dapoxetine and such medicinal products is required.

Effects of co-administered medicinal products on Dapoxetine hydrochloride

In vitro studies in human liver, kidney, and intestinal microsomes indicate Dapoxetine is metabolized primarily by CYP2D6, CYP3A4 and flavin monooxygenase 1 (FMO1). Therefore, inhibitors of these enzymes may reduce Dapoxetine clearance.

CYP3A4 inhibitors concomitant use of Dapoxetine and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and ata-zanavir, is contraindicated.

CYP2D6 inhibitors

Caution is advised if increasing the dose to 60 mg in a patient taking potent CYP2D6 inhibitors or if increasing the dose to 60 mg in a patient known to be a CYP2D6 poor metabolizer**.**

4.6 PREGNANCY AND LACTATION

It is not indicated for use by women. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy or embryonal/foetal development.

It is not known if they are excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

They have minor or moderate influence on the ability to drive and use machines. Dizziness, disturbance in attention, syncope, blurred vision and somnolence have been reported in subjects receiving Dapoxetine in clinical trials. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery. Combining with alcohol may increase alcohol− related neurocognitive effects and may also enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol.

4.8 UNDESIRABLE EFFECTS

Cellulite, influenza, sinusitis, Fluid retention, Headache, Migraine, tremor, Anaesthesia, Burning sensation, Hypothesizer, Retinal haemorrhage, Visual disturbance, Blurred vision, Photo phobia, Eye irritation, Red eyes, Insomnia, Anxiety, Agitation, Rest-lessness, Libido decreased, Abnormal dreams, Somnolence, Disturbance in attention, Tinnitus, Flushing, Sinus congestion, Yawning, diarrhoea, Dry mouth, Vomiting, Constipation, Abdominal pain, Dyspepsia, Flatulence, Stomach discomfort, Abdominal distention, Hyperthyroidism, Erectile dysfunction, Fatigue, Irritability, Blood pressure increased.

4.9 OVERDOSE

No case of overdose has been reported. In cases of overdose, standard supportive measures should be adopted as required. Due to high protein binding and large volume of distribution forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Sildenafil: The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide (NO) by inhibiting Phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation. Dapoxetine: Dapoxetine exhibits its efficacy by primarily inhibiting the reuptake of the serotonin transporter. It was also shown to bind and inhibit the reuptake transporters of dopamine & norepinephrine.

5.2 PHARMACOKINETIC PROPERTIES

Sildenafil

Absorption: Sildenafil citrate is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (range 25-63%). Its pharmacokinetics are dose-proportional over the recommended dose range. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state.

Distribution: When taken with a high fat meal, the rate of absorption is reduced. It is widely distributed into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal iso-enzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

Excretion: After oral administration, sildenafil is excreted as metabolites predo-minantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

Dapoxetine:

Absorption: Dapoxetine is rapidly absorbed with maximum plasma concentrations (Cmax) occurring approximately 1-2 hours after tablet intake. The absolute bioavailability is 42% (range 15 76%). Ingestion of a high fat meal modestly reduced the Cmax (by 10%) and modestly increased the AUC (by 12%) of Dapoxetine and slightly delayed the time for Dapoxetine to reach peak concentrations. It can be taken with or without food.

Distribution: More than 99% of Dapoxetine is bound to human serum proteins. The active metabolite desmethyldapoxetine (DED) is 98.5% protein bound.

Metabolism: Dapoxetine is cleared by multiple enzyme systems in the liver and kidneys, primarily CYP2D6, CYP3A4, and flavin monooxygenase (FMO1). There was evidence of presystemic first pass metabolism after oral administration. Intact Dapoxetine and DapoxetineN-oxide were the major circulating species in the plasma. Additional metabolites include desmethyldapoxetine and didesmethyldapoxetine, which account for less than 3% of the circulating medicinal product related material.

Elimination: The metabolites of Dapoxetine were primarily eliminated in the urine as conjugates. Unchanged active substance was not detected in the urine. Dapoxetine has a rapid elimination, as evidenced by a low concentration (less than 5% of peak) 24 hours after dosing.

5.3 PRECLINICAL SAFETY DATA

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ingredients	**Specification***
Microcrystalline Cellulose	BP
Lactose	BP
Maize Starch	BP
Croscarmellose Sodium	USNF
Colloidal Anhydrous Silica	BP
Magnesium Stearate	BP
Hydroxypropylcellulose	BP
Hypromellose (E 15)	BP
Polyethylene Glycol (6000)	USNF
Titanium Dioxide	BP
Talc	USP
Purified water	BP
Colour Brilliant Blue FCF Lake	IH
Isopropyl Alcohol	BP
Dichloromethane	BP
Colour Indigo Carmine Lake	IH

6.2 INCOMPATIBILITIES

No effect noted to date.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light & moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

The finished product Sildenafil and Dapoxetine Tablets is supplied in a Blister Packing. The pack size is 10 x 1 x 4 Tablets packed in a Blister.

6.6

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7. MARKETING AUTHORIZATION HOLDER:

UNOSOURCE PHARMA NIGERIA LTD
47 Babapomile Street, Onipetesi
Estate, Mangoro-Lagos, Nigeria

8. NAME AND ADDRESS OF THE MANUFACTURER

AKUMS DRUGS & PHARMACEUTICALS LTD.
Plot No. 19, 20 & 21, Sector 6A IIE, SIDCUL, Ranipur,
District: Haridwar, Uttarakhand INDI