NAME OF THE MEDICINAL PRODUCT

PALGRA JELLY

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 gm sachet contains:

Sildenafil Citrate equivalent to Sildenafil--------- 100 mg

UNIT COMPOSITION FORMULA	
NAME OF THE PRODUCT	**PALGRA JELLY** (Sildenafil Oral Jelly 100 mg) (Flavour : Orange)
GENERIC NAME:	**Sildenafil Citrate 100 mg Oral Jelly**

Approved Chemical Name	Quantity Per Sachets (5 gm)	Reason For Inclusion Of Ingredient	Specification

Sildenafil Citrate Eq. to Sildenafil #	0.149	Active	IH
Sucrose Pulverized	4.12	Sweetening agent	BP
Methyl Paraben Sodium	0.1919	Antimicrobial preservative.	BP
Propyl Paraben Sodium	0.00105	Antimicrobial preservative.	BP
Acesulfame Potassium	0.159	Sweetening agent	BP
Sodium Chloride	0.0265	Pharmaceutical aid.	BP
Propylene Glycol	0.318	Pharmaceutical aid.	BP
Sorbitol 70 %	1.105	Pharmaceutical aid.	BP
Sodium Carboxy Methyl Cellulose	0.0795	Pharmaceutical aid.	BP
Citric Acid	0.023	Pharmaceutical aid.	BP
Col. Sunset Yellow	0.00055	Colouring Agent	IH
Flavour Orange RSV15215	0.0265	Flavouring Agent	IH
Purified Water	Q.S.	Vehicle	BP

: 1.4048 mg OF SILDENAFIL CITRATE = 1mg OF SILDENAFIL

PHARMACEUTICAL FORM

Orange coloured homogenized jelly with weet taste and pleasant odour.

CLINICAL PARTICULARS

Therapeutic indications

Sildenafil Oral Jelly is indicated for the treatment of erectile dysfunction

Posology and method of administration

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, Sildenafil Oral Jelly may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

The following factors are associated with increased plasma levels of sildenafil: age > 65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance < 30 mL/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Ritonavir greatly increased the systemic level of sildenafil in a study of healthy, non-HIV infected volunteers (11-fold increase in AUC, see DRUG INTERACTIONS.) Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg of Sildenafil Oral Jelly in a 48 hour period.

Sildenafil Oral Jelly was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

When Sildenafil Oral Jelly is co-administered with an alpha-blocker, patients should be stable on alpha- blocker therapy prior to initiating Sildenafil Oral Jelly treatment and Sildenafil Oral Jelly should be initiated at the lowest dose.

Contraindications

Consistent with its known effects on the nitric oxide/cGMP pathway, Sildenafil Oral Jelly was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

After patients have taken Sildenafil Oral Jelly, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately

440 ng/mL). In the following patients: age > 65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatinine clearance < 30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.

Sildenafil Oral Jelly is contraindicated in patients with a known hypersensitivity to any component of the tablet.

Pregnancy and lactation

Not Applicable

Effects on ability to drive and use machines

None known.

Undesirable effects

Effects of Other Drugs on Sildenafil Oral Jelly

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.

In vivo studies: Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with Sildenafil Oral Jelly (50 mg) to healthy volunteers.

When a single 100 mg dose of Sildenafil Oral Jelly was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In addition, in a study performed in healthy male volunteers, coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with Sildenafil Oral Jelly (100 mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC. Sildenafil Oral Jelly had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in sildenafil clearance when it was coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine) . In another study in

healthy male volunteers, coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with Sildenafil Oral Jelly (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1000% (11-fold) 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 dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil Oral Jelly had no effect on ritonavir pharmacokinetics.

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.) with endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil Cmax. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma levels of sildenafil.

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

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, Ndesmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Effects of Sildenafil Oral Jelly on Erectile Response: In eight double-blind, placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections (RigiScan), after Sildenafil Oral Jelly administration compared with placebo. Most studies assessed the efficacy of Sildenafil Oral Jelly approximately 60 minutes post dose. The erectile response, as assessed by RigiScan , generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of Sildenafil Oral Jelly on Blood Pressure: Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.4/5.5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg of Sildenafil Oral Jelly, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates .Effects of Sildenafil Oral Jelly on Cardiac Parameters: Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Studies have produced relevant data on the effects of Sildenafil Oral Jelly on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.

The results from this pilot study are shown in Table 1; the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values

for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure and cardiac output decreased by 28%, 28%, 20% and 7% respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2 to 5 times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

TABLE 1. HEMODYNAMIC DATA IN PATIENTS WITH STABLE ISCHEMIC HEART DISEASE AFTER IV ADMINISTRATION OF 40 MG SILDENAFIL

Means ± SD	At rest				After 4 minutes of exercise			
	n	Baseline (B2)	n	Sildenafil (D1)	n	Baseline	n	Sildenafil
PAOP (mmHg)	8	8.1±5.1	8	6.5±4.3	8	36.0±13.7	8	27.8±15.3
Mean PAP (mmHg)	8	16.7± 4	8	12.1±3.9	8	39.4±12.9	8	31.7±13.2
Mean RAP (mmHg)	7	5.7±3.7	8	4.1± 3.7	-	-	-	-
Systolic SAP (mmHg)	8	150.4±12.4	8	140.6±16.5	8	199.5±37.4	8	187.8±30.0
Diastolic SAP (mmHg)	8	73.6 ± 7.8	8	65.9 ± 10	8	84.6 ± 9.7	8	79.5 ± 9.4
Cardiac output (L/min)	8	5.6 ± 0.9	8	5.2 ± 1.1	8	11.5 ± 2.4	8	10.2 ± 3.5
Heart rate (bpm)	8	67 ± 11.1	8	66.9 ± 12	8	101.9±11.6	8	99.0± 20.4

In a double-blind study, 144 patients with erectile dysfunction and chronic stable angina limited by exercise, not receiving chronic oral nitrates, were randomized to a single dose of placebo or Sildenafil Oral Jelly 100 mg 1 hour prior to exercise testing. The primary endpoint was time to limiting angina in the evaluable cohort. The mean times (adjusted for baseline) to onset of limiting angina were 423.6 and 403.7 seconds for sildenafil (N=70) and placebo, respectively. These results demonstrated that the effect of Sildenafil Oral Jelly on the primary endpoint was statistically non-inferior to placebo.

Effects of Sildenafil Oral Jelly on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in photo transduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of Sildenafil Oral Jelly on visual acuity, intraocular pressure, or pupillometry.

None stated.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sr. No.	Approved Chemical Name	Specification
1)	Sucrose Pulverized	BP
2)	Methyl Paraben Sodium	BP
3)	Propyl Paraben Sodium	BP
4)	Acesulfame Potassium	BP
5)	Sodium Chloride	BP
6)	Propylene Glycol	BP
7)	Sorbitol 70 %	BP
8)	Sodium Carboxy Methyl Cellulose *	BP
9)	Citric Acid	BP
10)	Col. Sunset Yellow	In house
11)	Flavour Orange RSV15215	In house
12)	Purified Water	BP

Incompatibilities

None stated.

Shelf life

36 Months

Special precautions for storage

Store at temp below 30ºC. Protect from light.

Keep out of reach of children

Nature and contents of container

50 sachets X 5gm & 10 sachets X 5gm, packed in a printed carton with a pack insert.

MARKETING AUTHORISATION HOLDER

- **Manufactured by:**

Navketan Pharma Pvt. Ltd. F-106,

M.I.D.C, Waluj, Aurangabad,

Maharashtra, India.

Marketed by: Pal Pharmaceuticals,

Plot 102, Maganda road,

Bompal industrial Area

Kano state

Nigeria

MARKETING AUTHORIZATION NUMBERS

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION :

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10. DATE OF REVISION OF THE TEXT :

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