PRESCRIBING INFORMATION

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

TADACCORD 20
(Tadalafil Tablets USP 20 mg)

1. BRAND OR PRODUCT NAME:

TADACCORD 20
Tadalafil Tablets USP 20 mg

2. NAME AND STRENGTH OF ACTIVE SUBSTANCE(S):

Tadalafil; 20 mg

3. PRODUCT DESCRIPTION:

Yellow, capsule shaped, biconvex, beveled edged, film coated tablets, debossed with "T 20" on one side and plain on the other side.

4. PHARMACOLOGICAL PROPERTIES:

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction. *ATC code:* G04BE08.

Mechanism of action
Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum.

Erectile dysfunction:
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 treatment of erectile dysfunction in the absence of sexual stimulation.

Pharmacokinetics Properties:

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) 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 TADACCORD 20 may be taken with or without food. The time of dosing (morning versus evening after a single 10 mg administration) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 litres, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours.

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
Over a dose range of 2.5 mg to 20 mg, exposure increases proportionally with dose Between 20 mg to 40 mg, a less than proportional increase in exposure is observed.

During tadalafil 20 mg and 40 mg once daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.5 fold of that after a single dose.

5. INDICATION:

Treatment of erectile dysfunction in adult males.

In order for TADACCORD 20 to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

TADACCORD 20 is not indicated for use by women.

6. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:
Erectile dysfunction in adult men:

In general, the recommended dose is 10 mg preferably taken with / without food prior to anticipated sexual activity.

In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of TADACCORD 20 (i.e., at least twice weekly) a once daily regimen with the lowest doses of TADACCORD 20 might be considered suitable, based on patient choice and the physician's judgment.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Special populations:

Elderly men
Dose adjustments not required in elderly patients.

Men with renal impairment:
Dose adjustment are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose for on-demand treatment.

Once-a-day dosing of 2.5 or 5 mg Tadalafil both for the treatment of erectile dysfunction is not recommended in patients with severe renal impairment (see sections 9 and 10).

Men with hepatic impairment:
For the treatment of erectile dysfunction using on-demand TADACCORD 20 the recommended dose of TADACCORD 20 is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety, of TADACCORD 20 in patients with severe hepatic impairment (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.

Once-a-day dosing of TADACCORD 20 both for the treatment of erectile dysfunction has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit /risk evaluation should be undertaken by the prescribing physician (see sections 9 and 10).

Men with diabetes
Dose adjustments are not required in diabetic patients.

Paediatric population
There is no relevant use of TADACCORD 20 in the-paediatric population with regard to the treatment of erectile dysfunction.

7. METHOD OF ADMINISTRATION

TADACCORD 20 tablet is for oral use. TADACCORD 20 may be preferably taken with / without food prior to anticipated sexual activity.

8 CONTRAINDICATION:

Hypersensitivity to the active substance or to any of the excipients listed in section 15.

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.

Tadalafil must 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 use of tadalafil is contraindicated in:

- 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 (<90/50mmHg), 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 ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

The co-administration of PDE5 inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

9. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before treatment with Tadalafil
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, and as such potentiates the hypotensive effect of nitrates.

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 who have undergone pelvic surgery.

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischaemic attacks, chest pain, palpitations and tachycardia, have been reported.

In patients who are taking alpha$_1$ blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. The combination of tadalafil and doxazosin is not recommended.

Vision
Visual defects and cases of NAION 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.

Decreased or sudden hearing loss
Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension and previous hearing loss history) patients should be advised to stop taking tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment
Due to increased tadalafil exposure, limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of tadalafil in patients with severe hepatic insufficiency (Child-Pugh class C). Once-a-day administration either for the treatment of erectile dysfunction has not been evaluated in patients with hepatic insufficiency. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis
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.

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).

Use with CYP3A4 inhibitors
Caution should be exercised when prescribing tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin)..

Tadalafil and other treatments for erectile dysfunction

The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take tadalafil in such combinations.

Lactose
Tadalafil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

10. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of Other Substances on Tadalafil
Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, i.e. ketoconazole Ritonavir, saquinavir, erythromycin, clarithromycin, itraconazole, and grapefruit juice, should be co-administered with caution, as they would be expected to increase plasma concentrations of tadalafil.

Transporters
The role of transporters (for example, p-glycoprotein) in the disposition of tadalafil is not known. Therefore, there is the potential of drug interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A CYP3A4 inducer, rifampicin, phenobarbital, phenytoin, and carbamazepine, may decrease plasma concentrations of tadalafil.

Effects of Tadalafil on Other Medicinal Products
Nitrates
Tadalafil is shown to augment the hypotensive effects of nitrates result of the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. In a patient prescribed any dose of Tadalafil (2.5mg - 20mg), where nitrate administration is deemed medically necessary in 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 administered under close medical supervision with appropriate monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8mg daily) and tadalafil (5mg daily dose and 20mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended.

Caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

5- alpha reductase inhibitors
Caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
The only pharmacodynamic effect was a small increase in heart rate. Although this effect is minor, it should be considered when co-administering these medicinal products.

Oral contraceptive pill
The increased concentration effect of ethinylestradiol is due to inhibition of gut sulphation by tadalafil.

Terbutaline
The increased concentration of terbutaline, probably due to inhibition of gut sulphation by tadalafil.

Alcohol
Alcohol concentrations were not affected by co-administration with tadalafil (10 mg or 20 mg). No changes in tadalafil concentrations were seen after co-administration with alcohol.

Cytochrome P450 metabolised medicinal products
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10mg and 20mg) had no clinically significant drug interaction with warfarin as vice versa.

Aspirin
Tadalafil (10mg and 20mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid.

11. FERTILITY, PREGNANCY AND LACTATION:

Pregnancy
It is preferable to avoid the use of Tadalafil during pregnancy.

Breastfeeding
Tadalafil should not be used during breast feeding.

Fertility
A decrease in sperm concentration was seen in some men.

12. UNDESIRABLE EFFECTS:

The most commonly reported adverse reactions in patients taking Tadalafil for the treatment of erectile dysfunction were headache, dyspepsia, back pain and myalgia, in which the incidences

increase with increasing dose of Tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

Organ System	**Adverse Reactions**
Immune system disorders	Hypersensitivity reactions
Nervous system disorders	Headache, Dizziness, Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Transient
Eye disorders	Blurred vision, Sensations described as eye pain Visual field defect, Swelling of Eye lids, Conjunctival hyperaemia.
Ear and labyrinth disorders	Tinnitus, Sudden hearing loss.
Cardiac disorders	Tachycardia, Palpitations, Myocardial infarction.
Vascular disorders	Flushing, Hypertension.
Respiratory, thoracic and mediastinal disorders	Nasal congestion, Dyspnoea, Epistaxis
Gastrointestinal disorders	Dyspepsia, Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux
Skin and subcutaneous tissue	Rash, Urticaria, , Hyperhydrosis (sweating)
Musculoskeletal and connective tissue disorders	Back pain, Myalgia, Pain in extremity
Renal and urinary disorders	Haematuria
Reproductive system and breast disorders	Prolonged erections, Priapism, Penile haemorrhage, Haematospermia.
General disorders and administration site conditions	Chest pain[1], Peripheral oedema, Fatigue, Sudden cardiac death[1]

[1] Most of the patients had pre-existing cardiovascular risk factors.

[2] More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Summary of the safety profile of Tadalafil in pulmonary arterial hypertension

The most commonly reported adverse reactions, were headache, nausea, back pain, dyspepsia, flushing, myalgia, naso-pharingitis and pain in extremity. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

13. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Tadalafil has negligible influence on the ability to drive or use machines. Patients should be aware of how they react to Tadalafil before driving or using machines

14. SIGNS & SYMPTOMS OF OVERDOSE AND TREATMENT:

In cases of overdose, standard supportive measures should be adopted, as required. Haemodialysis contributes negligibly to tadalafil elimination.

15. LIST OF EXCIPIENTS:

Core tablet
Lactose monohydrate
Microcrystalline Cellulose
Croscarmellose sodium
Hydroxy Propyl Methyl Cellulose
Sorbitan stearate
Magnesium stearate

Film-coating
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Iron oxide yellow (E172)
Triacetin
Talc

16. STORAGE CONDITIONS:

Store below 30 °C.
Keep out of the reach and sight of children.

17. DOSAGE FORMS AND PACKAGING AVAILABLE:

TADACCORD 20 mg tablets available in Clear PVC/PE/PVDC-Alu. blisters of 4 Tablets.

18. SHELF LIFE:

36 months.

19. NAME AND ADDRESS OF MANUFACTURER / MARKETING AUTHORIZATION HOLDER:

Manufacturer
Intas Pharmaceuticals Limited

Plot No. 457, 458 & 191/218P,
Sarkhej-Bavla Highway,
Matoda, Sanand, Ahmedabad,
Gujarat, IN-382210, India.

Product Registration Holder
Accord Healthcare Sdn. Bhd.
26-6 Menara 1 MK, Kompleks One Mont' Kiara,
No. 1 Jalan Kiara, Mont' Kiara,
50480 Kuala Lumpur, Malaysia

20. DATE OF REVISION:

02/03/2021