On March 21st, 2016, the Union Health Minister, Shri J P Nadda, launched Bedaquiline – new anti-TB drug for Drug Resistant TB as part of the RNTCP. Bedaquiline is being introduced at six identified tertiary care centres across India. Bedaquiline has been released specifically to treat multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (See approved indications for use below).

The safety and effectiveness of bedaquiline were established in 440 patients in two phase-2 clinical trials. The last time a drug was introduced specifically for the treatment of TB was in the late 1960s. That drug was rifampicin. Since then, resistance to rifampicin has been increasingly reported in the world. This is a major concern given that it remains among the most effective anti-TB drugs available today.

Mechanism of action
This new class of drug is a diarylquinoline that specifically targets Mycobacterial ATP synthase, an enzyme essential for supply of energy to Mycobacterium tuberculosis and most other mycobacteria. ATP synthase is a critical enzyme in the ATP synthesis of M. tuberculosis. Binding of bedaquiline to the oligomeric and proteolipic subunit-c of mycobacterial ATP synthase leads to inhibition of ATP synthesis, which subsequently results in bacterial death.

Adverse effects
1. Increased risk of death: About 11.4% of patients taking Bedaquiline died during clinical trials compared with 2.5% of those taking placebos. As the drug carries some significant risks, it is mandated to be used only in patients who do not have other treatment options.
2. Cardiac arrhythmias: Bedaquiline can affect the heart's electrical activity causing prolongation of the QT interval, which could lead to an abnormal and potentially fatal heart rhythm.
3. Interactions with other drugs, especially lopinavir and efavirenz (used in the treatment of HIV), ketoconazole, as well as other drugs used in the treatment of MDR-TB (eg moxifloxacin, clofazimine) may be expected.

For these reasons, the WHO and the FDA have approved bedaquiline as part of combination therapy to treat adults with MDR pulmonary TB only when other alternatives are not available.

Approved indications for use (WHO recommendations)
Up to now, bedaquiline has only been approved for use in patients who have MDR-TB and when options to treat this condition using existing drugs have been exhausted (either all fluoroquinolone and/or all second line injectables and extensive drug resistant TB, also known as XDR-TB). The drug is to be given in addition to the multidrug treatment regimen recommended by WHO.

Given the limited experience on its use, bedaquiline is recommended for use in adults affected with pulmonary (lung) MDR-TB. Special caution is needed when the drug is used in the elderly, in pregnant women, and in persons living with HIV who are taking antiretroviral medication. Bedaquiline should not be used to treat latent TB infection.

Sources:
3. WHO guidelines, Frequently asked questions, Bedaquiline available at http://www.who.int/tb/challenges/mdr

Fluoroquinolone use and the risk of aortic aneurysm
Fluoroquinolones are well known to be associated with tendon rupture and this is attributed to the antibiotics causing collagen breakdown. According to research from the University of Toronto, Canada, fluoroquinolone use is also associated with an increased risk of aortic aneurysm. A study of 1.7 million patients aged 65 years and over, published in BMJ Open (Nov, 2015), found that, within 30 days of finishing a course of treatment, patients who received fluoroquinolones were 2.2 times more likely to experience aortic aneurysm than other patients. The team concluded that according to the data, fluoroquinolone prescriptions can contribute acutely to aneurysm progression and rupture.

Source: CMC Pharmacy Bulletin, a publication of the Pharmacy Service (DISH), CMC, Vellore.
Inhaled steroids for asthma does not increase fracture risk
A systematic review, published in BMJ Open (Nov, 2015), found no association between inhaled corticosteroid (ICS) use lasting one to four years and fractures. Among 18 observational and randomized controlled studies involving patients with asthma, researchers found no link between ICS and the risk of fractures, nor with bone mineral density loss. Researchers say the findings should provide reassurance to prescribers.

Animal studies link painkiller use with infertility in females
Painkiller use in pregnancy may reduce fertility in subsequent generations, an animal study led by the Medical Research Council (MRC) centre for Reproductive Health at the University of Edinburgh and published in the journal Scientific Reports, has found. Preclinical tests in rats found that when a mother was given painkillers during pregnancy, her female offspring had fewer eggs, smaller ovaries and smaller litters of babies than those not exposed to the drugs. Exposed male offspring also had smaller numbers of cells that give rise to sperm in later life even though their reproductive function recovered to normalcy by adulthood. The effects of the drugs were seen within one to four days of the start of treatment. The study also demonstrated the effects in the subsequent generation of rats. The granddaughter rats of the experimental mother rat also had smaller ovaries and altered reproductive function.

This is probably due to the action on prostaglandins which are known to regulate female reproduction and control ovulation, the menstrual cycle and the induction of labour. The findings are significant, say the researchers, given the similarities between the reproductive systems of rats and humans. The team recommends that pregnant women should stick with current guidelines to use painkillers at the lowest possible dose and for the shortest possible time.

Is vitamin K different from vitamin K1?
What’s the difference between Vitamin K and K1? Vitamin K is a fat soluble vitamin and is generally used as a supplement; as antidote to drug induced hypoprothrombinemia; or prophylaxis and treatment of haemorrhagic disease of the newborn. Vitamin K works by promoting the hepatic formation of active prothrombin (factor II), factor VII, IX and X. Vitamin K formulations are classified into 5 subtypes (vitamins K1, K2, K3, K4 and K5) based on their source and/or method of preparation. Vitamin K1 is named as phytomenadione/phylloquinone and is prepared from natural sources. Vitamin K2 refers to a group of compounds (menaquionones) synthesized by bacteria in the intestinal tract. However, the amount synthesized does not usually satisfy the vitamin K requirement. The synthetic forms (water soluble) of vitamin K are vitamins K3 (menadione), K4 (menadiol) and K5. Menadiol is converted in the body to menadione. Since the synthetic water soluble forms (menadiol) do not require bile salts for absorption, they may be used for the prevention of vitamin K deficiency in patients with malabsorption syndromes in whom oral phytomenadione may be inefficiently absorbed. The fat soluble natural vitamin K (phytomenadione) is nontoxic even when large amounts are consumed orally and is recommended preparation for vitamin K supplementation. Though synthetic vitamin K (menadione) can cause toxicity and is not recommended to treat vitamin K deficiency, it continues to be used widely in developing countries like India because of less cost and easy availability. Most countries have switched to Phytonadione since early 1950s when hemolysis due to high doses of menadione was reported. So, what’s the difference between Vitamin K and K1? Vitamin K may mean any one of K1 to K5. K1 is simply phytonadione. CMC has Vitamins K1 in injection and tablet form and K3 only in injection form.

Confusion on keeping drugs cool is common
Patients are often confused by looking at the storage conditions mentioned on the product. The product pack recommended that the medicine to be stored in a cool temperature but not to be refrigerated. Proper storage of medications is always an important consideration during periods of extreme cold or heat. Here are few terms related to medicine storage and what they mean.

Store at 2 to 8°C: some products are very heat sensitive but must not be frozen. These are usually kept in the first and second part of the refrigerator (never the freezer).

Keep cool: store between 8 to 15°C (refrigeration is not required). In India, this may not be possible and hence may have to refrigerate them.

Store at room temperature: store at 15 to 25°C. If storage condition not specified, store the medicine at controlled room temperature (15°C to 30°C).