SAFETY ALERT

DRAP SAFTEY ALERT NO. 19

SUSPENSION OF REGISTRATIONS OF IRRATIONAL DRUGS COMBINATION (PARACETAMOL 500MG, THIORIDAZINE 3MG AND CAFFEINE 70MG).

UPDATE FROM REGISTRATION BOARD, PAKISTAN.

Date: 15th of June, 2022

Target Audience:

- Provincial Drugs Control Units and Provincial Pharmacovigilance Centres;
- Manufacturers of irrational drugs combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70MG);
- Healthcare Professionals; and
- Patients, consumers or caregivers.

Problem or Issue:

The Registration Board of Drug Regulatory Authority of Pakistan (DRAP) in its 317th meeting held on 16-17th of May 2022 in light of foregoing discussions, benefit-risk analysis and public health impact suspended all drug registrations of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) under Section 7 (11) (b, c & d) read with Section 42 of the Drugs Act, 1976 in the larger public interest, with immediate effect as this combination is neither approved by any Reference Regulatory Authorities nor safety and efficacy data is available with the registration holders. These formulations will stay suspended for a period of one (01) year; or till the time its safety and efficacy is well established through indigenous clinical trials in accordance with the Bio Study Rules, 2017; or if it is approved by the Reference Regulatory Authorities, whichever is earlier. Likewise, Registration holders were directed to suspend the manufacturing and import of these drug products immediately and to withdraw available stocks from the market in the larger public interest.

Background:

The Registration Board in its 263rd meeting held on 28th and 30th November, 2016 had decided that "*the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) is not available in any of the reference regulatory authorities as approved by the Board i.e. FDA, TGA, EMA, PMDA, MHRA, Health Canada, Germany, France, Switzerland, Sweden, Norway, Denmark, Austria and Netherland. Since it is reported vide WHO newsletter no.1, 2005 about the voluntary withdrawal of Thioridazine worldwide by the brand leader Novartis, hence all irrational combinations containing Thioridazine, which are also not existent worldwide be also withdrawn throughout the country.*

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Show cause notice will be served by the concerned Registration section after confirming international availability"

In 293rd meeting held on 6th-8th January, 2020, the board was informed that show-cause notices were served to registration holders. Later on, M/s. Wilson Pharmaceutical, Islamabad filed a case in the Court of Senior Civil Judge (West) Islamabad. The Court vide their order dated 01-11-2018 rejected plaint under order VII rule 11 of CPC.

Meanwhile, Provincial Drug Inspector, Nowshera on account of safety and efficacy concerns and the decision made in 263rd meeting of the Drug Registration Board seized the said drug combination product from multiple sales outlets at district Nowshera and then served a show-cause notice to M/s. Wilson, Islamabad. The General Manager of M/s. Wilson Pharmaceuticals Islamabad replied to him that the registration of Diagesic-P Tablet (Reg.No.015654) is still intact and renewed regularly from the DRAP and no proceeding regarding the cancellation/de-registration of Diagesic-P Tablet is initiated by DRAP. He had, therefore, requested for the final decision by DRAP in the case to further proceed in the matter.

Registration Board in its 293rd meeting held on 6-8th of January, 2020 deliberated on the matter in detail and decided to give an opportunity of personal hearing as per Drug Act, 1976 and Rules framed there under to both registration holders. In their reference Shifa international hospital also seconded the decision of the 263rd meeting that *"in the best interest of patient safety it is requested that company is to be directed by DRAP to remove this medicine Thioridazine from its combination product Diagesic-P. as its brand Melliril has been voluntarily recalled by Novartis due to serious cardiac side effects and later many other countries suspended its usage/ registration or imposed restrictions for use."*

Accordingly, in 313th meeting of the Registration Board it was discussed *"that as show-cause notices have already been issued to M/s Wilson Pharmaceuticals, Islamabad and M/s Cirin Pharmaceuticals (New Title: ICI Pakistan Ltd.), Hattar, therefore, Registration Board decided that management of abovementioned firms shall be given the opportunity of personal hearing in the forthcoming meeting of the Board under section 42 of the Drugs Act, 1976."*

Personal hearing before the Registration Board in its 317th meeting was granted on 17th May, 2022 at 10:00 A.M, wherein the board in light of the discussion of personal hearing, risk-benefit analysis and public health impact of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) decided to suspend all drug registrations of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) under Section 7 (11) (b, c & d) read with Section 42 of the Drugs Act, 1976 in the larger public interest, with immediate effect as this combination is neither approved by any Reference Regulatory Authorities nor safety and efficacy data is available with any registration holder for a period of 1 year or earlier subject some conditions.

Therapeutic Goods Affected.

Name: Combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg)
Brand Names: **Diagesic P** of Wilson's Pharmaceutical Islamabad; and
Pregesic of Cirin Pharmaceutical Hattar (Now ICI Pakistan).

Drug Combination (Paracetamol 500mg, Thioridazine 3mg & Caffeine 70mg) is routinely prescribed by physicians as an analgesic and is commonly sold by pharmacies and medical stores.

Advice for patients.

Patients and consumers are informed that the Registration Board of Drug Regulatory Authority of Pakistan (DRAP) in its 317th meeting held on 16-17th of May 2022 in light of discussions, benefit-risk analysis and public health impact suspended all drug registrations of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) under Section 7 (11) (b, c & d) read with Section 42 of the Drugs Act, 1976, therefore, patients who are using Drug Combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) may consult/ speak with their healthcare professionals for other treatment options available in the market.

Advice for healthcare professionals.

Healthcare professionals are informed that the Registration Board of Drug Regulatory Authority of Pakistan (DRAP) in its 317th meeting held on 16-17th of May 2022 in light of discussions, benefit-risk analysis and public health impact suspended all drug registrations of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) under Section 7 (11) (b, c & d) read with Section 42 of the Drugs Act, 1976 in the larger public interest, with immediate effect as this combination is neither approved by any Reference Regulatory Authorities nor safety and efficacy data is available with the registration holders. Healthcare professionals may stop prescribing to patients the Drug Combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg). Healthcare professionals may prescribe other treatment options available in the market as analgesics to the patients.

Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any adverse events they have experienced during their past treatment with Drug Combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) to **the National Pharmacovigilance Centre,** Drug Regulatory Authority of Pakistan through **DRAP Med Vigilance E-reporting system** or at npc@dra.gov.pk

Similarly, adverse events can also be reported through **Med Safety Mobile Application** that is available for download from the App store (For iOS devices) and Google Play (For Android devices).

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References:

1. Partial Minutes of 317th Meeting of Registration Board.