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Editorial

Greetings from Drug Information Bulletin!

Recent move by the Ministry of Health & Family Welfare Govt. of India prohibiting 14 Fixed Dose Combination (FDC) vide several S.Os dated 2nd June 2023 is a welcome step considering the wellbeing of the health of the people. A few years back DCGI published a list of FDCs as irrational, but those were available in the market as a result of some litigation. Again DCGI has given a direction to submit Safety and Efficacy data of the FDCs available in the market without approval from the DCGI with a deadline on 30th August 2013. After 2013 there were several exercise by the DCGI and ultimately they have banned about 344 irrational combinations vide S.O. 705 (E) to 1048(E) dated 10.03.2016 and S.O. No. 1851 (E) to 1855 (E) dtd. 08.06.2017. This is a unique occasion that a huge number of drugs have been banned by the Indian regulators. These moves made some of the pharmaceutical manufacturers in an uncomfortable position and they went to the court of law. The Hon'ble Supreme Court of India in its judgment stated that Central Government may carry out an inquiry and central Govt. has constituted a committee, who has submitted their report to the Govt. and DTAB subsequently. On the basis of the recommendations of the Expert Committee and the Drugs Technical Advisory Board, the Central Government is satisfied that it is necessary in public interest to regulate by way of prohibition for human use of the said drug in the country and prohibited 14 FDCs vide several S.Os dated 2nd June 2023.

As per the sources this step is a welcoming step to the healthcare professionals and several health activist groups who are fighting against huge number of irrational FDCs in the Indian market in the interest of the people.
DCGI has clarified the procedure for testing of Cough syrups for export

Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
FBI Bhawan, Kotla Road, New Delhi-110002

Date: 25th, May, 2023

To,
All State Drug Controllers/UTs
All CDSCO Zonal, Sub-Zonal, Port offices,
All Indian Drug manufacturers Associations

Subject: - Procedure for submission of cough syrups to be exported by the manufacturer/authorised person of manufacturer/exporter directly to any of the Central/NABL State accredited laboratories for testing purpose-reg.

Ref:- 1. Notification no. 06/2023 dated 22nd May, 2023
2. D.O. Letter No. X-11035/40/2023-DRS dated 23.05.2023

Sir,

Ministry of Commerce & Industry, Government of India vide Notification no. 06/2023 dated 22nd May, 2023 shall be permitting export of cough syrups, subject to the export sample being tested and production of Certificate of Analysis (CoA) issued by any of the Central Government Laboratories and any NABL accredited State Drug Testing Laboratory. Accordingly, Joint Secretary (R) MoH&FW, Government of India issued D.O. letter No. X.11035/04/2023-DRS on dated 23rd May, 2023 to all State Drug Controllers to actively engage with the manufacturer/export houses and relevant associations to ensure that this process goes smoothly.

In order to facilitate the process of testing of cough syrups at the said laboratories the following are the pre-requisite/requirements for submission of samples by the manufacturer directly to the nearby NABL accredited State / Central laboratories as mentioned in the notification issued by the Department of Commerce (Ref.1):

1. Covering letter from the manufacturer/exporter on letter head addressed to concerned laboratory.
2. Manufacturing license of the product for export purpose.
3. Export order.
4. Representative sample from the export consignment.
5. Thrice the quantity required for performing complete analysis of the sample.
6. Qualitative composition of product including excipients.
7. Certificate of analysis by the manufacturer of the particular batch and method of analysis (STP).
8. Reference/working standard (with traceability certificate) and Placebo as applicable.

In view of above, all State Licensing Authorities/CDSCO Zonal, Sub-Zonal Offices and all Indian Drug Manufacturer Association are requested to percolate the above requirements to all concerned who intend to export cough syrups.

Yours faithfully,

(Dr. Rajeev Singh Raghuvanshi)
Drugs Controller General (India) &
Central Licensing Authority

Copy to:

1. The Drugs Controller for the State of
   Gujarat/Karnataka/Kerala/Madhya Pradesh/Maharashtra/Jammu & Kashmir and Uttarakhand,
2. All Directors of NABL accredited State Laboratories of
   Gujarat/Karnataka/Kerala/Madhya Pradesh/Maharashtra/Jammu & Kashmir and Uttarakhand,
3. Secretary-cum-Scientific Director, IPC, Ghaziabad,
4. Head of laboratories of CDL, Kolkata,
5. Head of laboratories of CDTL, Chennai, Mumbai and Hyderabad,
6. Head of laboratories of RDTL, Guwahati, Chandigarh.

With a request to test DEG/EG in all samples even if it is not part of the manufacturer specifications along with other test parameters and issue the test report as per the format enclosed.
Ministry of Health Govt. of India has prohibited 14 Fixed Dose Combinations (FDC) vide notification dated 2nd June 2023

1. Nimesulide + Paracetamol dispersible tablet
2. Amoxicillin + Bromhexine
3. Pholphencine + Promethazine
4. Chlorpheniramine maleate+ Dextromethorphan+ Guaiaphesin+ Ammonium chloride+ Menthol
5. Chlorpheniramine maleate+ Codeine syrup
6. Ammonium chloride+ Bromhexine+ Dextromethorphan
7. Bromhexine+ Dextromethorphan+ Ammonium chloride+ Menthol
8. Dextromethorphan+ Chlorpheniramine + Guaiaphesin+ Ammonium chloride
9. Paracetamol+ Bromhexine+ Phenylephrine+ Chlorpheniramine+ Guaiaphesin
10. Salbutamol+ Bromhexine
11. Chlorpheniramine+ Codeine phosphate+ Menthol syrup
12. Phenytoin+ Phenobarbitone sodium
13. Ammonium chloride+ Sodium citrate+ Chlorpheniramine maleate+ Menthol syrup
14. Salbutamol+ Hydroxyethyltheophylline (Etofylline)+ Bromhexine

New FDC (Tremelimumab+ Durvalumab) injection, for intravenous use
Approval: 2022 (US FDA)

INDICATIONS AND USAGE: IMJUDO is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody indicated in combination with Durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).

DOSAGE AND ADMINISTRATION:
- Administer IMJUDO as an intravenous infusion over 60 minutes after dilution. uHCC:
  - Weight 30 kg and more: IMJUDO 300 mg as a single dose in combination with durvalumab 1,500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks
  - Weight less than 30 kg: IMJUDO 4 mg/kg as a single dose in combination with durvalumab 20 mg/kg at Cycle 1/Day 1,

DOSAGE FORMS AND STRENGTHS:
- Injection: 25 mg/1.25 mL (20 mg/mL) solution in a single-dose vial.
- Injection: 300 mg/15 mL (20 mg/mL) solution in a single-dose vial.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS:
- Immune-Mediated Adverse Reactions
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immunemediated nephritis with renal dysfunction and immune-mediated pancreatitis.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose.
  - Withhold or permanently discontinue based on severity and type of reaction.

- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue treatment based on the severity of the reaction.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

ADVERSE REACTIONS: Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritus, musculoskeletal pain, and abdominal pain. Most common laboratory abnormalities (≥ 40%) of patients with uHCC are AST increased, ALT increased, hemoglobin decreased, sodium decreased, bilirubin increased, alkaline phosphatase increased, and lymphocytes decreased.

USE IN SPECIFIC POPULATIONS: Lactation: Advise not to breastfeed.

Source: US FDA
**Status in India:** As per industry sources CDSCO has recently approved the same and it is expected that the same FDC will be available in India at a lower price very soon.

**Tigecycline Risk of coagulopathy**
The CDSCO has approved the recommendation from the NCC-PvPI, IPC to revise the PIL for tigecycline to include coagulopathy as an adverse drug reaction. Tigecycline is indicated for the treatment of skin and abdominal infections. The NCC-PvPI, IPC reviewed three ICSRs of tigecycline associated coagulopathy and a causal relationship between them was found. Reference: Based on the communication from IPC, India, October 2022 (link to the source within ipc.gov.in)

**Denosumab Potential risk of severe hypocalcemia in patients on dialysis**
The US Food and Drug Administration (FDA) is investigating the potential risk of severe hypocalcemia with serious outcomes, including hospitalization and death, in patients with advanced kidney disease on dialysis treated with denosumab (Prolia®). The US FDA is alerting health-care professionals and patients of these potentially serious risks as the investigation is going on. Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and men at high risk for bone fracture. There is a warning in the product information of the increased risk of hypocalcemia in patients with severe renal impairment or receiving dialysis. The US FDA’s review of interim results from an ongoing safety study of denosumab suggests an increased risk of hypocalcemia in patients with advanced kidney disease. Preliminary results from a separate internal study by the US FDA further investigating hypocalcemia in dialysis patients treated with denosumab show a substantial risk with serious outcomes, including hospitalization and death. Health-care professionals should consider the risks of hypocalcemia with the use of denosumab in patients on dialysis. When denosumab is used in these patients, adequate calcium and vitamin D supplementation and more frequent blood calcium monitoring, may help decrease the likelihood or severity of these risks. Patients on dialysis should be advised to seek help immediately, if they experience symptoms of hypocalcemia. Reference: FDA News Release, US FDA, 22 November 2022 (link to the source within www.fda.gov)

**The Institute of Biologicals (NIB) has been notified as statutory Lab for In-vitro diagnostics medical devices**

**Corrigendum to the last issue**
Under heading Pfizer issued warning on four products due to manufacturing defect four products was mentioned in their brand names. The composition are mentioned here- Magnex (Cefoperazone + Sulbactam), Zosyn (Piperacillin and Tazobactam), Magnamycin (Cefoperazone) and Magnex Forte(Cefoperazone + Sulbactam)

**DISCLAIMER:**
The Newsletter intends to provide updated and reliable information on medicines and other related issues in an attempt to equip healthcare professionals to take informed decision in recommending medicines to the patients. However, they are encouraged to validate the contents. None of the people associated with the publication of the Newsletter nor the organization shall be responsible for any liability for any damage incurred as a result of use of contents of this publication. The brand names of medicines, if mentioned, are for illustration only and the Newsletter does not endorse them.