Executive Summary: Association of Physicians of India: Position Statement on Role of Chirally Pure Molecules in Clinical Practice

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A. Chiral molecules

- Chiral molecules (derived from Greek word ‘cheir’ that stands for ‘hand’ or handedness) or enantiomers, are molecules that are non-superimposable mirror images of each other (similar to the left and right hand) and comprise a chiral center (usually a carbon, nitrogen, phosphorus or sulfur atom).¹
- They are classified as
  - rectus (R)- or sinister (S)-enantiomers based on atomic mass and number
  - levo (l) or dextro (d) based on rotation of plane polarized light and
  - cis or trans based on the position of functional group around the double bond

The mixture of two enantiomers is known as a racemate.²

B. Advantages of chirally pure drugs

- Single enantiomers or chirally pure drugs exhibit different bioactivity and metabolism as compared with the racemate. They may exhibit better receptor affinity, higher therapeutic activity, better safety profiles, less drug-drug interactions, reduced metabolic load and different pharmacological mechanism of actions and may have their distinct hepatic and renal excretion pathways.¹,³,⁴
- Chiral switching is development of single enantiomers from racemic mixtures that are previously approved and marketed.⁵

C. Regulatory considerations

- The registration process for approval of chirally pure molecules in India is

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similar to the category of new drugs as per schedule Y. 

- India currently follows the International Conference on Harmonization of Technical Requirements Q6A guidelines for ensuring quality of marketed chirally pure molecules similar to that of new chemical entities. 

D. Chirally pure drugs in therapy

Some important chirally pure molecules currently used in different areas of clinical practice include the following:

Cardiology
- **S-metoprolol** (an enantiomer of metoprolol) with a higher affinity for β1 receptor, demonstrated a 13.6% increase in responders (at day 21) at the dose of 50 mg as compared with racemate (100 mg). Similar results of blood pressure reduction were observed in hypertensive patients with co-existing illnesses such as chronic obstructive pulmonary disease, angina, angina co-existent with/without diabetes mellitus, and congestive heart failure without major safety concerns.
- **S-amlodipine** (an enantiomer of amlodipine) with a lower dose (2.5 mg) demonstrated a response rate of 92.7% as compared with 5 mg amlodipine (88%). The incidence of pedal edema was lower with S-amlodipine as compared with amlodipine.

Gastroenterology
- **S-omeprazole** (or esomeprazole, an enantiomer of omeprazole), exhibited higher bioavailability and less inter-patient variability as compared to omeprazole. The odds ratio of maintaining intragastric pH >4 with esomeprazole versus omeprazole was 1.57 (confidence interval=1.04, 2.38; p=0.03).

Neuropsychiatry
- Escitalopram (S-enantiomer of citalopram, selective serotonin reuptake inhibitor) demonstrated early onset of efficacy (within 2 weeks) and reduced the risk of relapse (over 36 weeks) of depression symptoms with less adverse events, in patients with major depressive and anxiety disorders as compared with citalopram. Additionally, the QTc interval prolongation of escitalopram was half as compared with citalopram.
- **S-zopiclone** (enantiomer of zopiclone, a sedative-hypnotic) displayed efficacy in the treatment of primary chronic insomnia, without the need for dose adjustment, in patients with renal failure as compared with zopiclone and revealed no substantial central nervous system depression.

Endocrinology
- **Levothyroxine** (an enantiomer of thyroxine) at lower doses (0.15 mg) demonstrated efficacy equivalent to dextrothyroxine (4 mg) for lowering of serum thyroid stimulating hormone, triglycerides, cholesterol and phospholipid levels in hypothyroid patients.
- **Myo-inositol (MI) and D-chiroinositol (DCI)** (both inositol isomers), used as insulin sensitizers, demonstrate beneficial effects at metabolic, hormonal, and ovarian level as therapy for polycystic ovarian syndrome. MI is the most abundant natural isoform of inositol whereas DCI is formed by epimerization of MI to DCI. Tissue-specific ratio of both exhibit different functions of these molecules. The combined administration of MI with DCI helps correct hormonal and metabolic imbalance.

Anesthesia
- As compared to its racemate, esketamine (S-enantiomer of ketamine), exhibited less disorientation, pain and fever in post-operative patients.
- **Levodopivacaine** (S-enantiomer of bupivacaine) revealed less cardiotoxic effects as compared to racemate.

Rheumatology, Pain, and Inflammation
- **S-etodolac** (enantiomer of etodolac) demonstrated 2.6 times higher potency and bioequivalence at half the dose when compared with the racemic mixture (300 mg vs 600 mg).
- **Dexketoprofen**, the S-enantiomer of ketoprofen displayed faster onset of action and efficacy at lower doses.

Pulmonology
- **R-salbutamol** (an enantiomer of salbutamol) and levocetirizine (R-enantiomer of cetirizine) displayed better safety profiles as compared to their racemates.

Infectious diseases
- **Levofloxacin** (active
S-enantiomer of ofloxacin, broad spectrum antibiotic, was more effective and safe in the treatment of multidrug-resistant tuberculosis, enteric fever, urinary tract infection and bacterial conjunctivitis as compared to ofloxacin.12-34

E. Recommendations for India

These recommendations aim to create awareness amongst regulatory bodies, clinicians, pharmacists, and patients on the use of chirally pure molecules in Indian clinical practice.

For regulatory bodies
- A different set of guidelines as compared to new chemical entities are required for the expedited approval of chirally pure molecules in India
- Providing a global perspective by generating awareness on guidelines governing the approval of chirally pure molecules in different countries

For clinicians
- General awareness of the concept of chirality and its effect on improving safety and efficacy outcomes in appropriate situations
- Awareness on the availability of chirally pure drugs with differential clinical and pharmacological profiles
- Awareness to be generated by continued medical education, concept-based panel discussions, and position statement and inclusion of clinicians in conducting clinical trials of chirally pure drugs

For pharmacists
- General awareness of the concept of chirality, particularly the key differences between racemates and enantiomers and its effect on the safety and efficacy outcomes under applicable conditions
- Understanding the sanctity of drug prescriptions
- Awareness could be increased by policy campaigns, education camps, and clinicians counselling the pharmacists on non-equivalence of drugs and discouraging substitution

For patients
- Realizing the importance of chirally pure drugs and its value in reducing the drug dosage and side-effects
- Information on safety and efficacy of chirally pure drugs to be disseminated via physician counselling, media campaigns and patient education forums
- Healthcare providers should readily share their knowledge and experience with patients on using chirally pure drugs

This executive summary will be followed by a position statement of API on chirally pure molecules in clinical practice elaborating every aspect alluded to in this summary.

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