MINUTES OF 50TH MEETING OF THE TECHNICAL COMMITTEE HELD ON 29.06.2022 AT 11:30 AM UNDER THE CHAIRMANSHIP OF DGHS FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN LIGHT OF DIRECTIONS OF THE HON'ABLE SUPRIME COURT OF INDIA ON 03.01.2013.

Present:

1. **Prof. (Dr.) Atul Goel,** — **Chairman**
   Director General of Health Services,
   Ministry of Health and Family Welfare.
2. **Dr.Yash Paul,** — **Member**
   Prof. & Head, Dept. of Cardiology,
   PGIMER, Chandigarh.
3. **Dr. B. L. Sherwal,** — **Member**
   Director, Rajiv Gandhi Super Speciality Hospital,
   Tahirpur, New Delhi - 110 093
4. **Dr.Kamlakar Tripathi,** — **Member**
   Prof., Dept. of Medicine,
   Institute of Medical Sciences,
   Banaras Hindu University, Varanasi – 221005.
5. **Dr. Ashok Kumar Das,** — **Member**
   Professor of Medicine & Professor and Head of Endocrinology,
   Pondicherry Institute of Medical Sciences, Pondicherry.
6. **Dr. Vibhu Mendiratta ,** — **Special Invitee**
   Professor & HOD Dept. of Dermatology ,
   Lady Harding Medical College , New Delhi.
7. **Dr. V. Dhir,** — **Special Invitee**
   Consultant Dept of Dermatology ,
   RML Hospital New Delhi.

8. **Dr. V.G. Somani ,** **CDSCO**

Drugs Controller General (India)

9. **Mr. A. K. Pradhan,** **CDSCO**

Joint Drugs Controller (India), .

The chairman welcomed the members of the committee for 50th Technical committee meeting. Thereafter, 6 proposals were placed before the committee for deliberation. The committee discussed the proposals one after another and gave its recommendation.

Agenda No. 1

APPLICATION FOR IMPORT AND MARKET PLAZOMICIN INJECTION 500 MG/10 ML (50 MG/ML) WITH LOCAL PHASE III CLINICAL TRIAL WAIVER AND PHASE IV COMMITMENT.

The details are as under:-

Product Name: Plazomicin injection 500 mg/10 mL (50 mg/ml)

Indication: Plazomicin is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli, Klebsiellapneumoniae, Proteus mirabilis, and Enterobacter cloacae.*

Global Approval Status:

- Received fast track status from US FDA in 2012 – Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
- Received Qualified Infection Disease Product (QIDP) designation (created by Generating Antibiotic Incentive Now [GAIN] which provides certain incentives for development of new antibiotics) in 2015.
- In 2017, US FDA granted the Breakthrough Therapy designation - A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
- Approved by USFDA in 2018 for treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s):
  E coli, K pneumoniae, Proteus mirabilis, and Enterobacter cloacae.

Approval Status in India: - Not yet approved by CDSCO.

Regulatory History in India:

Cipla had applied for grant of permission to import and market Plazomicin injection 50 mg/ml with a Phase III CT waiver and commitment of Phase 4 study in India. The proposal was deliberated in the SEC meeting dated 26th Nov 2021. The committee did not recommend for a local clinical trial waiver and opined that the firm should conduct a Phase III clinical trial in the country.

Thereafter, M/s. Cipla applied for deliberation of their proposal to the Technical Committee and request for grant of permission to import and market Plazomicin injection 50 mg/ml with a local Phase III clinical trial waiver and with a Phase IV commitment.

Justification for local Clinical Trial waiver submitted by the firm

- Provision of New Drugs & Clinical Trial Rules 2019, Rule 75, clause 7 of which states that:
  provided there is no probability of evidence of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug and no major unexpected serious event being reported, requirement of local clinical trial can be waived provided applicant undertakes to conduct local Post Marketing Phase IV study for said new drug.

As per firm's submission:

Summary	
Clause	**Response**
(i) the new drug is approved and marketed in countries specified by the Central Licencing Authority under rule 101 and if no major unexpected serious adverse events have been reported	USFDA approved in 2018 and no new risks and major safety concerns since approval for Plazomicin.
(iii) there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug	India was part of the Global Phase 2 Clinical Trial where 42 subjects were enrolled form India. Phase 2 Pharmacokinetic study done in Indian patients demonstrated that differences in Plazomicin exposure are not clinically significant, and no dose adjustment is necessary for Indian patients (Submitted to as a part of dossier).The clinical outcomes and safety profile for Indian subjects were comparable to the overall study population.

(iv) the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licencing Authority	Committed for Phase 4 study
The local clinical trial may not be required to be submitted along with the application referred to in sub-rule (1) if,(iii) **where the drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India** such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug	• Complicated UTI is one of the common infections and with rising antimicrobial resistance, the common uro pathogens like *E. coli have developed resistanceto commonly used antibiotics such as piperacillin tazobactam*(resistance rate 47%). • Carbapenem resistance is increasing amongst enterobacteriacea and commonest mechanism of carbapenem resistance in *E. coli* is MBL production (NDM). UTI caused bycarbapenem-resistant Enterobacteriaceae (CRE) is associated with high mortality (40 - 50% in critically ill patients). • Currently available antibiotics in India do not cover all the resistance mechanisms (ESBL/NDM/OXA-48) of *E. coli.* • Newer antibiotic such as ceftazidimeavibactum does not have activity against MBL producing Enterobacteriacea. • Aminoglycosides are recommended by Indian guidelines (ICMR 2019 andGuidelines for Antibiotic Prescription in Intensive Care Unit). [3]However, resistance rate to commonly used aminoglycosides such as amikacin is 19%, the commonest resistance mechanism being inactivation by aminoglycoside modifying enzymes (AME). • Plazomicin is a novel aminoglycoside which due to structural modification maintains its activity against majority of AMEs. It has shown to have good in-vitro activity against AME producing Enterobacteriaceae, CRE (MBL, Oxa 48, KPC), ESBL producing Enterobacteriaceae and colistin resistant

	Enterobacteriaceae.as well. Thus, it caters to unmet need in AMR era. • Plazomicin will be an important treatment optionforcUTI • Plazomicin due to its activity against resistant pathogens may aid as *carbapenem and colistinsparing agent* which may further aid in minimizing spread of AMR.

Note: Safety, Efficacy and Pharmacokinetics data for Plazomicin in Indian patients with cUTI is available as Indian study centers in the Global Phase 2 Clinical Trial.

- Antimicrobial resistance is a serious and growing threat to the world. WHO's global surveillance of antimicrobial resistance reveals that antibiotic resistance is no longer a prediction for future and is putting the ability to treat common infections in the community and hospitals at risk.

- WHO in collaboration with the Department of Biotechnology released the list of Indian priority pathogens in 2020. The critical priority pathogens include Carbapenem, Tigecycline and Colistin resistant Enterobacteriaceae (*K. pneumoniae and E. coli*) and Carbapenem and Colistin resistant non-fermenting bacteria -*A. baumannii and P. aeruginosa*.

- Worldwide, urinary tract infections (UTIs) are some of the most common bacterial infections, affecting 150 million people each year and in India prevalence ranges from around 21.8 to 31.3 %. *E. coli* (Enterobacteriaceae) is the most common causative pathogen (>80%) associated with complicated UTI (cUTI).Across-sectional study conducted in south India, included 500 patients with signs and symptoms of UTI and/or with UTI confirmed by urine culture, admitted in hospital. Results showed prevalence of cUTIwas 76.80% and *E. coli* was the commonest organism identified in cUTI patients.

- The ICMR Guidelinesand Guidelines for Antibiotic Prescription in Intensive Care Unit recommend aminoglycosides for the treatment of cUTI.Aminoglycosides, such as amikacin, gentamicin are commonly used for treatment of cUTI, however they often harbour AME encoding gene. AMEs are most common resistance mechanism observed among Aminoglycosides, thus making them ineffective against AME forming *E. coli. Other recommended antibiotics include Beta lactam/Beta lactamase inhibitors (BL/BLI) and carbapenems.* Carbapenems are being used especially in the treatment of MDR gram negative infections.

- According to ICMR's AMR surveillance report 2020, the susceptibility rates of *E. coli* against aminoglycoside (amikacin), carbapenem (Meropenem) and BL/BLI- Piperacillin Tazobactam) were 81%, 76% and 47% respectively.

- The Carbapenem Resistant Enterobacteriaceae (CRE), has been a major concern in India, as carbapenemase production is the commonest cause of resistance to carbapenems and MBL (especially NDM) enzymes are majorly responsible for carbapenem resistance in *E. coli.*

- cUTI caused by CRE is associated with high mortalityrate (40-50%). With rising prevalence of CRE, the last resort of antibiotics like polymyxins are being used in treatment of these difficult to treat infections.

- Currently there are very limited antibiotic option available in India for treating cUTI due to CRE. The newly introduced antibiotics in India such as ceftazidime avibactam have no activity against MBL (NDM). Thus, there is urgent need for antibiotic which has activity against MDR as well as carbapenem resistant *E. coli*. This may aid in sparing carbapenems and colistinin treatment of cUTI caused by these resistance pathogens.

- Plazomicin (plazomicinsulfate) is a novel, semisynthetic compound derived from chemical modification of the natural product sisomicin, which provides protection against common aminoglycoside modifying enzymes (AMEs), that inactivate other drugs from aminoglycoside class. These chemical modifications increase the activity of plazomicin against isolates harbouring AMEs.

- Plazomicin has good in-vitro activity against AME producing Enterobacteriaceae, CRE (MBL, Oxa 48, KPC), ESBL producing Enterobacteriaceae and colistin resistant Enterobacteriaceae as well. Plazomicin has good coverage against aminoglycoside resistant Enterobacteriaceae.

- Five-year trends on the susceptibility of enterobacterales to plazomicin and other aminoglycosides in hospitals in the US during 2016 to 2020. Results showed that susceptibility rates against CRE for plazomicin increased from 96.3% in 2016 to 100.0% in 2020 (97.3% overall) and were markedly higher than amikacin (75.2% overall), gentamicin (48.7%), and tobramycin (11.1%).

- Plazomicin displayed potent activity against colistin-resistant clinical enterobacterial isolates, including those expressing the mcr-1 gene. In study, Plazomicin inhibited 89.5% and 93.7% of CRE isolates at≤2 and ≤4mg/L. **Plazomicin was more active than other aminoglycosides (amikacin, gentamicin and tobramycin) against colistin-resistant enterobacterial isolates.**

- Pre-clinical study has shown relatively lower incidence of nephrotoxicity as compared to other aminoglycosides. Non-clinical PK investigations of plazomicin showed that PK, distribution, metabolism, and excretion are similar to those reported for other aminoglycosides.

- Plazomicin has convenience of once daily dosing compared to other aminoglycosides and BL/BLIs (TID dosing).

- Phase II study demonstrated that in patients with cUTI or AP, plazomicin was noninferior to levofloxacin in microbiological eradication, clinical outcomes, and was generally well tolerated. **This global study was conducted in US, India, Colombia, and Chile, and included a total of 42(29%) adult subjects from India.**

- Phase III EPIC trial with 609 patients with cUTI including acute pyelonephritis demonstrated that once dailyplazomicin (15 mg/kg) was non-inferior to meropenem (1 g every 8 hours) in treatment of cUTI and acute pyelonephritis patients caused by Enterobacteriaceae, including MDR strains. The primary efficacy endpoint was composite cure which was 81.7% in Plazomicin group and 70.1% meropenem group.Also, **Plazomicin showed lower rate of microbiological (3.7 % vs 8.1%) and clinical relapse (1.6 % vs 7.1%) as compared to meropenem at late follow up.**

- Another, Phase III CARE evaluated the comparative efficacy and safety of plazomicin (15 mg/kg) against colistin (300 mg loading; 5 mg/kg/d divided q8h or q12h) in CRE infection patients. Trial results showed that **Plazomicin was associated with lower mortality (14% vs 53 %) and less SAE than colistin (50% vs 81%)**. Fewer patients in the plazomicin group than in the colistin group had a clinically meaningful increase (≥0.5 mg per deciliter) in the serum creatinine concentration at any time during the trial (16.7% vs 50%). The study concluded that Plazomicincan be used in patients with serious infections caused by MDR Enterobacteriaceae who have limited treatment options.

- **Indian Data -**

  - **Phase II global trial**
    In global Phase II study of 145 patients conducted in US, India, Colombia, and Chile, **a total of 42 adult subjects from India were included (29% of the total sample).**Analysis comparing the pharmacokinetic parameters of Indian subjects and non-Indian subjects demonstrated that differences in plazomicin exposure were not clinically significant between two groups and no dose adjustment is necessary for Indian patients. Post-hoc analysis also evaluated clinical and microbiological outcomes in Indian patients which showed

Plazomicin was well tolerated and demonstrated similar microbiological and clinical response in Indian patients with cUTI or AP. The clinical outcomes and safety profile were comparable to the overall study population(Connolly LE et al. 2018).

- ***In -vitro study – (CMC Vellore)***
  An in-vitro study conducted at CMC, Vellore, India to determine MIC, molecular resistance mechanisms and estimate the bactericidal activity of plazomicin by using time kill studies in carbapenem susceptible and resistant MDR gram-negative Indian clinical isolates. The study demonstrated that 91% and 67% of MDR and Carbapenem resistant E coli were susceptible to Plazomicin. Plazomicin had better activity than PIP/TAZ (33%) and maintaining its susceptibility against other aminoglycoside (gentamicin) resistant *E. coli*(72%). Time kill assay showed plazomicin synergy with meropenem (against both *E. coli and K. pneumoniae*)and PIP/TAZ (against *K. pneumoniae*).

- **Post marketing safety data** - Since its approval (2018) there have been no major safety concerns since approval. No new risks were identified during the period. Therefore, the benefit–risk assessment previously established for plazomicin remains unchanged since the launch of the product.

Broad spectrum antibiotics play an invaluable role in the treatment of bacterial infections, there are some drawbacks to their use, such as spread of resistance across multiple bacterial species, detrimental effect upon the host microbiome, and eradication of commensal gut bacteria which can result in colonization by the opportunistic pathogen *C. difficile*. Targeted antibiotic therapy may not select for cross-resistance in non-targeted pathogens and elicit abrogated or reduced collateral damage upon the host microbiome. There is need of using step down therapy to target antibacterial agents that exhibit selectivity for a particular genus or species and has the potential to overcome some of these issues particularly in MDR bacterial infections and where recurrence is common. Hence it is critical that along with broad spectrum antibiotics targeted antibiotics acting against specific bacteria be made available.

- Plazomicin is a targeted antibiotic indicated for treatment of cUTI including pyelonephritis due to Enterobacteriaceae, caused by the following susceptible microorganism(s): *Escherichia coli, Klebsiellapneumoniae, Proteus mirabilis, and Enterobacter cloacae.*
- Plazomicin has been listed as a 'Reserve Antibiotic' along with other antibiotics such as colistin, fosfomycin, polymyxin B, ceftazidime + avibactam and etc by the WHO (WHO EML 22nd List, 2021). WHO recommends this

group includes antibiotics and antibiotic classes which should be reserved for treatment of confirmed or suspected infections due to MDR organisms. They should be reserved for treatment of "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant Enterobacteriaceae. India is reporting very high rates of carbapenem resistance amongst the commonest uropathogen*E. coli* (CDDEP data), and hence there is an urgent need to make this drug available in in India for treating these difficult infections.

- Plazomicin caters to unmet need in current AMR scenario in India, in terms of activity against resistant uro-pathogens. It has shown good in-vitro activity against ESBLs producing and MDR Enterobacteriaceae, CRE and colistin resistant Enterobacteriaceae as well. It has greater activity compared to PIP/TAZ and ceftazidime with convenience of once daily dosing. Also, plazomicin has shown synergistic activity with meropenem (against both *E. coli and K. pneumoniae*) and PIP/TAZ (against *K. pneumoniae*) in in-vitro studies.

- Plazomicin will be an important antibiotic in the treatment of cUTI caused by resistant Enterobacteriaceae. It may be useful as a carbapenem sparer or colistin sparer which may aid in minimizing spread of AMR.

Summary:

- ✓ Plazomicin is US-FDA approved in 2018 for treatment of cUTI including pyelonephritis caused by *E. coli, K. pneumoniae, P. mirabilis, and E. cloacae.*
- ✓ *In-vitro data has* good in-vitro activity against resistant Enterobacteriaceae (AME, CRE [MBL/Oxa 48/KPC] ESBL, colistin resistant). Indian in-vitro studies conducted at CMC Vellore, India showed good activity against MDR/CR *E. coli.*
- ✓ In addition to the in-vitro microbiological data, human, safety, efficacy and pharmacokineticshas been evaluated in Indian patients (Global Phase 2 study) and showed no differences between the Indian and non-Indian population.
- ✓ Plazomicin has been listed as a 'Reserve Antibiotic' by WHO and would cater to the unmet need in management of cUTI and AP caused by resistant Enterobacteriaceae.It may act as carbapenem or colistin sparer thus minimising spread of AMR.

- A local Phase III study would result in prolonging the availability of Plazomicin injection by approximately 2-2.5 years and thereby would deprive Indian patients of this reserve treatment option which can address the serious issue of antimicrobial resistance.

Based on the above points and with reference to New Drugs and Clinical Trials Rules, 2019, Chapter X - Import or Manufacture of New Drug for Sale or for Distribution, Rule 75 the firm request for marketing authorization for Plazomicin injection 500 mg/10 mL (50 mg/mL) with a Phase III clinical trial waiver and the firm committed for conducting a phase IV study in India which can help in accelerating the availability of Plazomicin in India.

Recommendations:

The firm presented their justification for Phase-III Clinical trial waiver before the technical committee.

The committee observed that justification presented for local clinical trial waiver was not adequate.

The committee after detailed deliberation recommended that the firm should submit detailed in-vitro study data conducted at CMC, Vellore including subset analysis of the Phase-II global clinical trial in Indian population to CDSCO for further review by the committee.

Agenda No. 2

APPLICATION FOR GRANT OF PERMISSION TO IMPORT AND MARKETING OF CRISABOROLE OINTMENT 2%.

The details are as under:-

File No: -ND/IMP/20/000098
Product name: - Crisaborole Ointment 2%
Firm name: -M/s Pfizer Products India Pvt. Ltd, purpose of application import & market.
The details submitted by the firm or as under:-

Approval Status Globally: -Crisaborole Ointment 2% [Staquis®]received first approval from US FDA on 14thDecember 2016post which it also received approval from Canada, European Union (27 member states), Australia, Colombia, China & Hong Kong.

Approval Status in India: - Not yet approved.

M/s Pfizer Products India Pvt. Ltd. submitted an application for grant of permission to import and marketing of Crisaborole Ointment 2%.Crisaborole ointment is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age & older.

The proposal of the firm was deliberated in the SEC (Dermatology and allergy) twice and recommendations are as under :-

Recommendations of the SEC (Dermatology & Allergy) held on 12.01.2021

The firm presented their proposal for import & market of the drug along with local clinical trial waiver before the committee. Committee noted that firm has presented inadequate data as well as justification for local clinical trial waiver as per requirements. After detailed deliberation, the committee recommended that the firm should conduct the phase III clinical trial and accordingly firm should submit the phase III clinical trial protocol to for further review by the committee.

Recommendations of the SEC (Dermatology & Allergy) held on 11.02.2021

In light of earlier recommendation dated 12-01.2021, the firm presented their proposal before the committee. After detailed deliberation committee reiterated its earlier recommendation dated 12.01.2021.

Therefore the firm's proposal for CT waiver was deliberated in 49th Technical committee dated 18.01.2022

Recommendation of 49th Technical committee dated 18.01.2022 are as under:-

After detailed deliberation the committee recommended for grant of permission to import and market Crisaborole ointment 2% subject to the Condition that the firm should conduct a phase IV clinical trial for which protocol should be submitted for review by the SEC within 3 months of approval of the drug.

In the meantime, a complain was received through DGHS, MoH&FW dated 30.03.2022 with a copy of mail received from Dr. Sanjay Yadav alleging that DCGI, violating the Rules and favoring the multinational pharmaceuticals. The complainant has stated that biased practice is being followed by DCG(I) in favoring MNC i.e. Pfizer, by approving local clinical trial waiver for Crisaborole ointment 2%for the treatment of Atopic dermatitis.

It was mentioned in the complain that various alternative drugs are available for atopic dermatitis and New drugs are being introduced without testing the safety and lack of available clinical data on Indian patient. Further as per NDCT Rules, waiver of local Phase III clinical study is permissible in conditions for only rare disease/life threatening treatment or for disease of special relevance to Indian health scenario or unmet need in India, however DCG(I) in his personal capacity under the umbrella of Technical committee review has favored and endorsed in providing waiver of Phase III study of new drug thereby compromising the effectiveness and acceptable safety profile in treating the disease.

It was also stated that previously the above proposal of clinical trial waiver has already been deliberated in SEC (Dermatology and allergy) in which the committee did not approve for waiver of local Phase III clinical trial.

Further, complainant has alleged that another formulation of M/s Sanofi for same indication i.e. Atopic dermatitis was deliberated in Technical Committee dated 24.04.2021, for waiver of conduct of Clinical trial however it was not accepted by Technical committee for Clinical Trial Waiver. Applicant has requested to look into the matter and take immediate action in this regard.

In addition , M/s Pfizer has also submitted their request for release of technical committee approval notification for Crisaborole -a global breakthrough drug for treatment of mild to moderate Atopic Dermatitis by stating that Pfizer is looking to launch its latest breakthrough therapy for atopic Dermatitis in India so that this medicine can be made available to patients in the country and further given following justification.

Crisaborole-Breakthrough drug for mild to moderate Atopic Dermatitis

- Noval, first in class, non-steroidal topical treatment option for management of mild to moderate Atopic Dermatitis (AD) for patients who are 2 years and older.
- As compared to existing steroidal treatments such as TCI, TCS, biologicalsets, can be used for a longer duration (upto 28 days) and can also be applied on sensitive skin areas such as face, intertriginous areas, genitals, flexor areas.
- Reduced element of safety risk in comparison to existing steroidal treatments.
- Crisaborole has been approved by major countries including USA, EU Canada, Australia, etc. and has had global market presence for more than 4 years.
- Skin & allergy Society has also acknowledged the need for introduction of newer and non-steroidal drugs with better safety outcomes.

And further Pfizer mentioned that they awaits final notification of DCGI approval and they had submitted the marketing authorization application for Crisaborole to DCGI on Nov 19, 2020.

Recommendation:

After detailed deliberation the committee opined that another oral drug with same mode of action (i.e acting of PDE 4) is available but committee is not satisfied with its efficacy after it's use for many years in various conditions like Psoriasis.

After detailed deliberation the committee recommended that the firm should submit the following details for further consideration :-

- **Details of results of Global Clinical Trial data.**
- **Name of countries where CT waiver have been granted and the drug Crisaborole Ointment 2% has been approved.**

Agenda No. 3

APPLICATION FOR PERMISSION TO IMPORT AND MARKET OF FIXED RATIO COMBINATION OF INSULIN GLARGINE AND LIXISENATIDE 100U + 50MG /33MG (SOLIQUA™ SOLOSTAR®)

The details are as under:-

File No. BIO/IMP/21/000043

Appl. Date - 31-MAY-2021

Name of Firm - M/s Sanofi Healthcare India Pvt. Ltd.

Drug Name - **Fixed Ratio Combination of Insulin Glargine and Lixisenatide 100U + 50µg /33µg (Soliqua™ Solostar®)**

Purpose of deliberation - Application for permission to **import and market** the new drug – regarding

M/s Sanofi Healthcare India Pvt. Ltd., has submitted application for Marketing authorization of Fixed Ratio Combination of Insulin Glargine and Lixisenatide 100U + 50µg /33µg (Soliqua™ Solostar®) for following indication:

Proposed Indication: Soliqua is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT2 inhibitors, when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product (sulfonylurea, glinide, DPP-4 inhibitors or gliptins, and Sodium-glucose co-transporter 2 (SGLT2)inhibitors or gliflozins) or with basal insulin or with glucagon-like peptide-1 (GLP-1) receptor agonist.

The individual drugs have been approved CDSCO and are currently marketed by Sanofi in India:

- Insulin Glargine inj. 100U has been approved vide approval dated 7thJan 2003 (Lantus®)
- Lixisenatide inj. 10 mcg and 20 mcg has been approved dated 15thJan 2015 (Lyxumia®)

Soliqua is available as a sterile solution for injection in prefilled pen in two dosage strengths. The product will be administered parenterally (subcutaneously).

Apart from various clinical studies conducted globally, firm has conducted 2 studies (one GCT and one India specific study) in India as below.

1. **Indian data on Soliqua™ in GCT:**

Multicentre, open-label parallel group randomized controlled trial to compare iGlarLixi versus premixed insulin in patients with type 2 diabetes who have failed to

achieve glycemic control with basal insulin and oral antidiabetic agents (Global Premix Study) (Global patients : 887 Indian patients : 182)

A total of 883 patients were exposed to open-label treatment (442 patients in the iGlarLixi group and 441 patients in the Premix BiAsp 30 group) and were included in the safety population.

Efficacy results: Both of the primary objectives of the study were met; when compared with Premix BiAsp 30, treatment with iGlarLixi showed statistical non-inferiority in terms of HbA1c reduction from baseline to Week 26 and statistical superiority in terms of body weight change.

From a mean value of 8.6 % at baseline in both treatment groups, HbA1c had fallen to 7.26% in the iGlarLixi group and 7.48% in the Premix BiAsp 30 group.

Statistical non-inferiority (margin 0.3 %) of iGlarLixi over Premix BiAsp 30 was demonstrated for the change in HbA1c from baseline to week 26 (LS mean difference [97.5% CI] versus Premix BiAsp 30: -0.24 [-0.41; -0.08] %; p<0.001).

At baseline, mean bodyweight was 80.7 kg in the iGlarLixi group and 82.2 kg in the Premix BiAsp 30 group. At Week 26 mean bodyweight had decreased by a LS mean of -0.7 kg with iGlarLixi and increased by a LS mean of 1.15 kg with Premix BiAsp 30. Superiority of iGlarLixi over Premix BiAsp 30 was demonstrated for the change in body weight from baseline to Week 26 (LS mean difference versus Premix BiAsp 30 -1.86 [95% CI: -2.28; -1.43] kg; p<0.001.

The results of this study show that once daily iGlarLixi provided a significantly better glycemic control with beneficial changes in body weight and less hypoglycemia when compared with twice-daily Premix BiAsp 30. iGlarLixi can provide an efficacious, simple, and well-tolerated alternative to premixed insulins as a means of intensifying therapy in patients whose T2DM is not controlled with basal insulin plus OAD

2. India specific study:

A randomized, 24-week, controlled, open label, parallel arm, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination (FRC) to insulin glargine in type 2 diabetes patients, inadequately controlled on Basal Insulin with or without Metformin (INSLIL08556) (Indian Patients: 247 patients)

This study was conducted in 13 sites across India from June 2018 to November 2019.

From a mean HbA1c at baseline of 8.27%, the HbA1c decreased by a mean of -0.79% in the FRC arm and -0.72% in the insulin glargine arm, reaching a level of 7.56% and 7.50% at week 24 respectively, both of which remained above threshold for control (HbA1c >7%). This change was statistically significant within each of the treatment arms (p value: <.0001).

The difference between the treatment groups was 0.01% (95% CI: -0.25, 0.27) and was not statistically significant (p-value: 0.9285) and hence the primary study objective to demonstrate the superiority of the FRC over insulin glargine in the change in HbA1C from baseline to week 24 was not met.

As with HbA1c, the difference between the treatment arms in the change from baseline to week 24 in FPG and 2h-PPG were not statistically significant.

There were no death/s in this study, no SAEs were reported and there were no AEs reported that led to patients withdrawing from the study.

Overall, the FRC was well-tolerated, and there were no new safety signals in any of the safety areas of interest. The safety profile of FRC treatment generally reflected the established safety profiles of its components. Both arms had good treatment compliance of over 99% each and the same duration of exposure.

Patterns at various layers of study execution, such as the high number of operational deviations, the lack of quality control in the central laboratory that processed the blood samples for the efficacy variables HbA1c, FPG and PPG, and the insufficient dose titrations not done according to protocol, across sites have directly impacted the validity of the efficacy results. Although it is not possible to entirely invalidate the study results, it is also not possible to validate them. Therefore, robust conclusions cannot be drawn from this study, i.e. the study is inconclusive on efficacy results. The review of safety data did not identify any new safety signals compared to established safety profiles of Soliqua and its components.

Details of recommendations of SEC are as under:-

- **On SEC (Endocrinology and Metabolism) 24.08.2021 & 25.08.2021**
  The firm presented their proposal for Marketing Authorization of the Fixed Ratio combination with clinical trial data generated globally and in India. However, the committee didn't recommend for grant of marketing authorization as the primary endpoint was not achieved in India specific trial with the Fixed Ratio combination. The minutes of the meeting are as follow:

  "The firm presented their proposal for marketing authorization of the Fixed Ratio combination with clinical trial data generated globally and in India.
  The committee noted that, the primary endpoint was not achieved in India specific trial with the Fixed Ratio combination.
  After detailed deliberation, the committee didn't recommend for grant of marketing authorization."

- **On SEC (Endocrinology and Metabolism) 21.12.2021 & 22.12.2021**, firm presented justifications and sub-group analysis of trial outcomes and for their proposal for grant of marketing authorization of the Fixed Ratio combination with clinical trial data generated globally and in India. However, the committee

reiterated its earlier decision and did not recommend for grant of marketing authorization for the product. The minutes of the meeting are as follow:

"In light of the SEC meeting dated 24.08.2021 & 25.08.2021, the firm presented justifications and sub-group analysis of trial outcomes and for their proposal for grant of marketing authorization of the Fixed Ratio combination with clinical trial data generated globally and in India.
After detailed deliberation, the committee reiterated its earlier decision and did not recommend for grant of marketing authorization for the product."

Accordingly, firm was informed SEC recommendation vide letter dated 31.01.2022.Now, firm has submitted application for appeal to Technical Committee meeting being aggrieved by the recommendations of SEC with following submission:-

1. **GCT Indian subgroup already meets regulatory requirements for approval:**

Phase III trial GCT LPS15017 was conducted with adequate Indian subjects (i.e. n=182, including 100 exposed to Soliqua).Soliqua demonstrates efficacy and good safety profile in Indian population, consistent with the overall benefit and risks observed worldwide.

2. **Local study (INSLIL08556) was inconclusive due to operational issues:** The Local Study was completed with 247 Indian patients. However, the efficacy results of this study are considered by Sanofi as not reliable due to 3 factors that had significant impacts on the efficacy outcomes:

- Potential errors in sample handling by the central laboratory raising questions regarding the validity of results produced for primary and key secondary efficacy parameters (HbA1c, FPG and PPG):
- Further high number of operational deviations were observed in study execution
- Insufficient titration following noncompliance to protocol algorithm.This directly impacted the efficacy outcome because the insulin dose in the FRC arm never caught up with the Insulin glargine arm all through the study, while the dose in the latter group continued to steadily increase over time.

These issues, across sites have directly impacted the validity of the efficacy results, and robust conclusions cannot be drawn from this study, i.e. the study is inconclusive on efficacy results. The review of safety data did not identify any new safety signals compared to established safety profiles of Soliqua and its components.

In summary, owing to the above, the Local Study was determined as inconclusive.

3. **Safety of Soliqua is demonstrated in Indian Patients:**

There were no new safety signals in any of the safety areas of interest in both studies. The safety profile of FRC treatment generally reflected the established safety profiles of its components.

4. **Soliqua is currently registered in more than 70 countries** including European Union, USA, Brazil, Japan etc. with a history of approved use in jurisdictions worldwide (first approved in US on 21 November 2016 in EU on 11 January 2017).

5. **Favourable Benefit-Risk Balance Soliqua offers the following advantages:**
   - Fasting+ post-prandial glucose control
   - Effective HbA1c reduction
   - More patients achieving glycemic targets
   - Mitigating weight increase of basal insulin
   - No additional risk of hypoglycemia versus basal insulin
   - Improved GI tolerability vs. GLP-1 receptor agonists (GLP-1RAs)
   - Cumulatively, there were approximately 3653 subjects (80 healthy subjects, 3573 patients) exposed to the fixed ratio combination in Marketing Authorization Holder sponsored clinical trials since the Development International Birth Date (09 April 2009).
   - The cumulative exposure to the fixed ratio combination was estimated to be 287 847 patient years from 01 January 2017 through 31 May 2021, including 61,998 patient years during the interval period from 01December 2020 through 31 May 2021.
   - The analysis of 182 Indian patients in the GCT demonstrated efficacy and safety results consistent to those from the overall study population.

6. **Sanofi proposes to conduct Phase IV Study:**

To complement existing data firm propose to conduct a Phase IV 26-week single arm post-approval study to generate additional efficacy data (primary objective) and safety data (secondary objective) in the same patient population.

In view of the above, firm request for permission to import and market the new drug with commitment to conduct a Phase IV study.

Remarks:

- GCT conducted with 182 Indian patients in which iGlarLixi versus Premix BiAsp 30 in patients showed statistical non-inferiority in terms of HbA1c reduction from baseline to Week 26
- The Local Study with 247 Indian patients was conducted comparing insulin glargine/lixisenatide (FRC) to insulin glargine in type 2 diabetes patients. However, the primary endpoint to demonstrate the superiority of the FRC over

insulin glargine in the change in HbA1C from baseline to week 24 was not met due to Potential errors in sample handling, high number of operational deviations and Insufficient dose titration.

- Firm presented justifications and sub-group analysis of trial outcomes and for their proposal with clinical trial data generated globally and in India before SEC. However, SEC didn't recommend for grant of marketing authorization as primary endpoint was not achieved in India specific trial with the Fixed Ratio combination.
- Firm requested for Technical Review Committee based on commitment to conduct a Phase IV study.

Recommendations:

The committee after detailed deliberation, recommended that, the firm should submit India specific data of the global clinical trial to CDSCO for further consideration by the committee.

Agenda No. 4

APPLICATION OF M/S ELI LILLY AND COMPANY (INDIA) PVT. LTD., FOR GRANT PERMISSION TO IMPORT AND MARKET THE DRUG IMPORT AND MARKETING OF BARICITINIB TABLETS 2 MG AND 4 MG INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMITITIES WHO ARE CANDIDATES FOR SYSTEM THERAPY (ADDITIONAL INDICATION) IN INDIA WITH PHASE III CLINICAL TRIAL WAIVER.

The details are as under:-

File No. SND/IMP/21/000001

Appl. Date - 26-JUN-2020

Name of Firm - M/s Eli Lilly and Company (India) Pvt. Ltd.

Drug Name - Baricitinib tablets 2 mg and 4 mg

Purpose of deliberation - Application in for grant of permission to Import and Market the drug for Sale and Distribution in India Baricitinib tablets 2 mg and 4 mg indicated for the treatment of adult patients with moderate to severe atopic dermitities who are candidates for system therapy (additional indication) in India

Regulatory Status in India:

Brand name/ Product name	Indication	Approval Date
Bariticinib Tablets 2mg & 4mg	for the treatment of moderate to severe active Rheumatoid arthritis in adult patients who have responded inadequate to, or who are intolerant to one or more disease modifying anti-rheumatic drugs. Baricitinib may be used as monotherapy or in combination with	07.05.2018

	Methotrexate	
	Baricitinib in combination with Remdesivir for treatment of suspected or laboratory conformed coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)	03.05.2021

The proposal of the firm was deliberated in 57th SEC (Dermatology & Allergy) meeting held on 09.06.2021 and the recommendations of the committee are as follows:

The firm presented the proposal of import and marketing of Baricitinib Tablets 2mg & 4mg indicated for the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy (additional indication), requesting clinical trial waiver.

After detailed deliberation the committee recommended that the firm should conduct a clinical study on clinically significant number of patients by excluding the patients with past history or on concurrent TB. Further, Photographs should be captured during the conduct of study. Accordingly, the firm should submit the Phase III clinical trial protocol to for review by the committee.

In continuation the firm had re-requested for waiver of animal toxicity study waiver.

Therefore, the proposal of the firm was deliberated in 60th SEC (Dermatology & Allergy) meeting held on 12.08.2021 and the recommendations of the committee are as follows:

In light of recommendations of earlier committee meeting held on 09.06.2021 the firm presented their proposal for reconsideration of clinical trial waiver.

After detailed deliberation, the committee re-iterated its earlier recommendations that "the firm should conduct a clinical study on clinically significant number of patients by excluding the patients with past history or on concurrent TB. Further, photographs should be documented during the conduct of the study. Accordingly, you should submit the Phase III clinical trial protocol to for review by the committee".

Subsequently the proposal was again deliberated in the SEC

Recommendation of SEC (Dermatology and Allergy) meeting held on 13.01.2021 are as follows:

In light of recommendations of earlier SEC meeting dated 12.08.2021, the firm presented their proposal for reconsideration of clinical trial waiver.

After detailed deliberation, the committee reiterated its earlier recommendation that

"the firm should conduct a clinical study on clinically significant number of patients by excluding the patients with past history or with concurrent TB. Further, photographs should be documented during the conduct of the study. Accordingly, the firm should submit the Phase III clinical trial protocol on statistically significant number of patients to for further review by the committee".

On 26.05.2022, the firm had appealed for deliberation in Technical Committee meeting being aggrieved by the recommendation of SEC with following justifications

1) Baricitinib Tablets 2mg & 4mg for Atopic Dermatitis indication approved and marketed in EU/EEA, Australia, Switzerland , Japan, Brazil , etc

Firm futer stated that additional Phase 3 Study excluding patients with past or current TB is not needed because:

- India has been part of 2 global phase III studies (14V-MC-JHL and I4V-MC-JANH) which was approved from .
- 14V-MC-JAHL (Multicentric , Randomised , Double Blind, Placebo – controlled , Phase 3 study to evaluate the efficacy and safety of Baricitinib in adult patients with moderate to severe atopic dermatitis)
    - Study completed , 9 centres in India is participated.
    - In the Indian subpopulation , A total 46 patients were randomised and analysed in the intent to treat population and safety population.
- I4V-MC-JANH (phase 3 Multicentre , double blind study to evaluate the Long term safety and efficacy of Baricitinib in Adult Patients with Atopic Dermatitis)
    - Study status: On going, 8 centres in India participated in the study.
    - In the Indian sub population , A total 31 patients were randomised and analysed in the intent to treat population and safety population.
- Current and completed trials of Baricitinib in patients with AD enrolled very few patients with past or latent TB and excluded patients with active TB, and
- Existing clinical trial data, including long-term data from study I4V-MC-JAHN (JAHN), support a positive benefit-risk profile of Baricitinib in the Indian population.

Recommendations:

The committee opined that the sample size for Indian sub population in the submitted global clinical trial is inadequate. Therefore, the committee opined that the firm should conduct Phase III Clinical trial in sufficient sample size for which the firm should submit the protocol to CDSCO.

Agenda No. 5

APPLICATION OF M/S. INVENTIA HEALTHCARE LIMITED FOR GRANT OF MANUFACTURING AND MARKETING PERMISSION OF FDC OF ACOTIAMIDE HYDROCHLORIDE HYDRATE (AS SUSTAINED RELEASE PELLETE) 300MG + RABEPRAZOLE SODIUM IP (AS ENTERIC COATED PELLETS) 20MG CAPSULES

The details are as under:-

Applicant: M/s. Inventia Healthcare Limited

Drug name: Fixed dose combination of Acotiamide Hydrochloride hydrate (as sustained release pellete) 300mg + Rabeprazole Sodium IP (as enteric coated pellets) 20mg Capsules

Type of Application: Manufacturing and Marketing

Proposed Indication: Indicated in the treatment of adult patients suffering from functional dyspepsia and GERD for treatment of bloating after meals, epigastric bloating and early satiety in functional dyspepsia and gastro esophageal reflux disease (GERD) not responding to proton pump inhibitor (PPI) alone.

Regulatory Status: FDC is not yet approved in any country.

Recommendations of SEC (Gastroenterology & Hepatology) held on 16.09.2021;

The firm presented their proposal before the committee. After detailed deliberation, the committee opined that:

1. The firm did not present adequate satisfactory scientific justification along with rationality w.r.t. proposed FDC.
2. It will be difficult to titrate the dose.
3. There are chances of misuse of FDC which will lead to undesirable side effects.
4. FDC is not approved anywhere in the world.
5. This FDC is not recommended in standard treatment guidelines. In view of above, committee did not recommend for approval of the FDC.

However, the firm had requested to place the proposal in upcoming Technical Committee meeting for deliberation.

Recommendation:- The committee opined that the data submitted by the firm with respect to safety and efficacy parameters is inadequate. Therefore the committee didn't recommend for grant of permission for manufacture & marketing of the FDC.

Agenda No. 06

APPLICATION FOR GRANT OF PERMISSION TO IMPORT AND MARKET DUPLIUMAB 150 MG/ML (300 MG IN 2 ML), SOLUTION FOR S.C INJECTION (PREFILLED SYRINGE AND PREFILLED SYRINGE WITH NEEDLE SHIELD) BASED ON LOCAL PHASE III CLINICAL TRIAL WAIVER - REG

The details are as under:-

F.No.: BIO/Form44/FF/2019/12911
F.No. BIO/IMP/19/000006
Firm Name - M/s Sanofi-Synthelabo (India) Private Limited
Date of application – 31.01.2019

It is stated that M/s Sanofi-Synthelabo (India) Private Limited submitted application on 31st January 2019 for grant of marketing authorization (permission to Import and market) for **Dupilumab (BRNAD name – Dupixent) 150 mg/ml (300 mg in 2 mL), solution for SC Injection (PFS and PFS with needle shield)**.

The drug is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical therapy.

Pack presentation - single-use pre-filled syringe with needle shield contains 300 mg dupilumab in 2 mL solution.

Recommended dose of Dupixent for adult patients - **initial dose of 600 mg** (two 300 mg injections), **followed by 300 mg given every other week**. Based on individual therapeutic response, the dosage may be increased to 300 mg given weekly

The proposal was deliberated in SEC twice and the recommendations were as under:-

1st SEC meeting held on 12th Sept 19 –

Firm presented their proposal for grant of marketing authorization with local clinical trial waiver. The committee opined that there was no clinical data available on this drug in Indian patients and alternative therapies are available for the proposed indication. After detailed deliberation, the committee recommended that the firm should conduct local Phase III clinical trial to assess the safety and efficacy profile of the drug in Indian patients and submit the protocol for review.

In-light of the minutes reproduced above, on **30th Sept 2019** the firm was informed to submit Phase-III CT protocol for taking further action in this regard.

On 8th Nov 2019, the firm submitted request for reconsideration of phase III waiver request in light of the New Drug and Clinical Trial Rules 2019 as specified in Chapter X Rule 75 (7) under provided criteria i, ii, iii and iv.

Based on firm's request, the matter was re-deliberated in the 44th SEC (Dermatology & Allergy) held on 17th January 2020

Recommendations of the said meeting is as follows –

*Firm presented its proposal for grant of marketing authorization with local Phase III clinical trial wavier. The committee noted that the proposal was earlier deliberated on **12.09.2019** wherein the committee recommended that the firm should conduct local Phase III clinical trial to assess the safety and efficacy profile of the drug in Indian patients and submit the protocol for review as there is no clinical data available on this drug in Indian patients and alternative therapies are available for the proposed indication. After detailed deliberation, the committee reiterated its recommendation as per the SEC meeting dated 12.09.2019. Accordingly, the firm should conduct local Phase III clinical trial to assess the safety and efficacy of the drug in Indian patients.*

Phase III clinical trial waiver was not considered in the Subject Expert Committee held on 12th Sept 2019 & 17th Jan 2020.

Therefore , the proposal was deliberated in **46th Technical committee held on 26.04.2021.**The recommendation of the meeting is as follows

"The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the firm should conduct local Phase III clinical trial to assess the safety and efficacy of the drug in Indian patients"

Subsequently, firm had made another appeal and has requested a Phase 3 clinical trial waiver again based on the following robust justification including additional supportive information/ data:

1) Dupixent is approved in over 60 countries worldwide and favorable safety profile has been observed in the post marketing phase . Its benefit risk profile continues to remain favorable. The first approval was in March 2017 in US for the treatment of adults with inadequately controlled moderate-to-severe AD. This was followed by an approval in the EU in September 2017. Apart from US and EU, Dupixent is also registered in Australia, Canada, Japan, UK and other countries worldwide.

2) Dupilumab is registered across all age groups from adults to pediatric and is proven to be safe and marketed even in children as young as 6 years of age.

3) Dupilumab clinical development studies were conducted in 23 countries and based on the robust data Dupilumab is registered in 60+ countries.

4) Dupilumab registration in 39 countries was granted without any local clinical data.

5) Dupixent was designated as "Breakthrough Therapy" by the US FDA during the review process and "Promising Innovative Medicine" (PIM) by MHRA.

6) Dupilumab was granted approval in China as an overseas medicine considered urgently needed in clinical practice, leading to a waiver of local clinical trial requirements and an expedited review and approval process.

7) Dupixent fulfils an Unmet Medical Need - Moderate-to-severe AD is a serious, chronic, debilitating skin disease with substantial impact on day to-day functioning and wellbeing of affected patients. It shares pathophysiological pathways with other atopic/allergic conditions such as asthma, allergic rhinitis, and food allergies, which are common comorbidities in patients with AD.

8) The currently available treatments for AD have important limitations including unsatisfactory effectiveness and important risks and side effects. These limitations result in a large number of patients with moderate-to-severe AD whose chronic disease cannot be safely controlled by the existing therapies.

9) Management with currently available therapies for Moderate to Severe AD is challenging. While a majority of patients with mild AD respond well to topical prescription therapy, many patients with moderate-to-severe disease cannot achieve adequate control with safe doses of topical medications. Systemic therapy is indicated in patients who do not respond adequately to topical therapies or when topical therapy is inadvisable. Existing systemic therapies include non-selective broad-acting immunosuppressants such as systemic corticosteroids, which can be associated with important side effects.

10) Moderate-to-severe AD is a serious chronic condition and effective therapies with an acceptable safety profile upon long-term use are currently not available.

11) Dupixent the first targeted biologic drug approved for moderate to severe AD and proven efficacy mild manageable side effects. Dupilumab IL-4 and IL-13 signaling mediated activation of their respective receptors. Both cytokines signaling pathways play roles the /immune disorders, which forms basis dupilumab's efficacy shown clinical studies atopic diseases such asthma, nasal polyposis and atopic dermatitis.

12) As per the European Public Assessment Report, Dupixent been shown reduce the extent and severity atopic dermatitis. The side effects of Dupixent are generally mild manageable. The European Medicines recommended approved assessment provided

13) Independent Publication in "Dermatology" Key Opinion Leaders Indian experience Key opinion leaders successfully treated 25 patients Dupilumab and published paper describing "Real-world effectiveness and Safety Dupilumab treatment of moderate Severe Atopic Dermatitis in Indian Patients: multicentric Retrospective Study' Indian Journal of Dermatology in June The authors observed significant efficacy, tolerability, and safety profile AD in clinical trials in the populations.

14) Extensive Evidence Real-World Experience: Dupixent approved for indications atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis in over countries worldwide. Three randomized, double-blind, placebo-controlled trials (SOLO 1, SOLO 2, and CHRONOS) enrolled a total of 2119 subjects 18 years of age older with moderate-to-severe atopic dermatitis (AD) not adequately controlled topical medication(s). Dupixent was shown to be safe and efficacious when used monotherapy and when concomitantly with TCS (topical corticosteroids steroids) in the treatment of adult patients with moderate-to-severe whose disease not adequately controlled with topical prescription therapies or when therapies are advisable.

15) As of 28th September 2021 (data lock point), 13062 subjects were enrolled into the development program and included the safety population. This includes 5011 patients from atopic dermatitis studies, 4091 from asthma studies, 782 from chronic rhinosinusitis with nasal polyposis, 428 from eosinophilic amongst others.

16) The number subjects exposed dupilumab clinical 10565 (4519 in atopic dermatitis studies, 3530 asthma studies, 470 chronic rhinosinusitis with nasal polyposis studies, 378 in eosinophilic esophagitis studies amongst others)

17) Based sales figures received WHP defined daily dose of 21.4 mg for Parenteral formulation, the cumulative exposure marketed experience could estimated to be 522786 patient from March 2017 through September 2021, including 148697 patient years during the interval period from 01st April 2021 through 30th September 2021.

18) Low ethnic sensitivity: Post Hoc Analysis from 3 phase III trials - As Dupilumab is a protein product, ethnic sensitivity is expected to be low. The PK of dupilumab is insensitive to ethnic factors, owing to the lack of involvement of non-catabolic pathways

19) Results from the Bridging Study Report between Asian and non-Asian population confirms the similarities in IL-4Ra target expression between ethnicities and indicates the saturation of target mediated clearance at the steady-state exposure at 300 mg q2w dose regimens

20) Dermatologists from the Skin Allergy Research Society (SAS) of India have requested Dupilumab to be made available for AD patients, of which many remain inadequately controlled in spite of many existing therapeutic options available. Attached is a letter from the SAS addressed to Sanofi

21) An access program has been initiated in India to provide the drug to needy patients. So far 18 patients have benefited from the access program.

22) Ongoing safety data from Ph 3 Global Study with 100 Indian patients in Asthma Indication. There is an ongoing Phase III global study (with INDIA) for the asthma indication "A randomized, double blind, placebo-controlled, parallel-group phase 3 study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma". Patient number: 10 centers/74 patients. F. No: CT/71/18-DCG(1). While the study report is awaited, firm has enclosed Line listing of adverse events, which indicates that no related adverse events or serious adverse events were observed in the Indian patients participating in the trial.

23) Dupilumab: A recent multidisciplinary consensus of AD experts recommended that duplumab be used as a first-line systemic treatment in adults with moderate-to-severe AD who are uncontrolled with topical therapies. This recommendation is based on the strong efficacy and safety data for dupilumab in comparison to the safety profiles of conventional systemic therapies that are not approved for use in AD (Encl 9). (Ref: Ariens, L., Bakker, D. S., van der Schaft, J., Garritsen, F. M., Thijs, J. L., & de Bruin-Weller, M. S. (2018). Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy. Therapeutic advances in chronic disease, 9(9), 159-170.)

24) Commitment to do phase IV study: As per Rule 75 (7) (iv), the firm has committed to conduct a ph IV study if we are given waiver of ph III local clinical study.

In view of the above evidences, and recently published independent Indian experience demonstrating the high unmet medical need and response to therapy in moderate to severe AD cases the, firm had requested for reconsideration of their case at the Technical Committee for grant of a phase III clinical trial waiver.

Recommendations: After detailed deliberation committee recommended that the firm should submit the complete clinical trial data for review.

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