MINUTES OF 47th MEETING OF THE TECHNICAL COMMITTEE HELD ON 19.02.2020 UNDER THE CHAIRMANSHIP OF DGHS FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA ON 03.01.2013.

Present:

1. **Prof. (Dr.) Rajiv Garg,** — Chairman
   Director General of Health Services,
   Nirman Bhawan, New Delhi
2. **Dr. Yash Paul Sharma,** — Member
   Prof. & Head, Dept. of Cardiology,
   PGIMER, Chandigarh.
3. **Dr. Kamlakar Tripathi,** — Member
   Former Prof., Dept. of Medicine,
   Institute of Medical Sciences, BHU, Varanasi.
4. **Dr. B. L Sherwal,** — Member
   Director, Rajiv Gandhi Super Speciality Hospital
   Tahirpur, New Delhi-110093

From CDSCO:

1. Dr. V. G. Somani,
   Drugs Controller General (India)
2. Dr. K. Bangarurajan,
   Joint Drugs Controller (India)
3. Mr. A. K. Pradhan,
   Deputy Drugs Controller (India)
4. Mr. Sanjeev Kumar,
   Deputy Drugs Controller (India)
5. Mr. Jayant Kumar,
   Deputy Drugs Controller (India)

The Chairman welcomed the members of the committee for the 47th Technical Committee meeting. Thereafter, total 13 proposals were placed before the committee for consideration. The committee discussed the proposals one after another and gave its recommendation. The details of the proposals and recommendation of the committee are as under:

Agenda No. 1

Proposal of M/s National Institute for Research in TB, Chennai for approval of Major Protocol amendment of study "STREAM Stage 2"- V 8.0 dated 13/04/18

Name of Applicant:. M/s. National Institute for Research in TB, Chennai

Drug Name/indication: Anti-tuberculosis drugs in MDR patient

Type of Application: Protocol amendment of study "STREAM Stage 2"- V 8.0 dated 13/04/18

Proposed Indication: Anti-tuberculosis drugs in MDR patients

Phase-IIIB

The STREAM Stage 2 study is a randomised global clinical trial aimed at evaluating novel standardised, shorter MDR-TB regimens. In India the trail started enrolment in India from Dec 2017 after approval from the CDSCO (Ref CT/48/15 dated 23.05.16) and HMSC (Ref 5/8/140/2016 ECD II dated 15.04.16).

Protocol Title: "STREAM The evaluation of a standard treatment of anti-tuberculosis drug for patients with MDR-TB for shortening of MDR-TB treatment-regarding (Study protocol number: ISRCTN 78372190, Version 6.2, dated Feb/15-approved initially).

Subject: The firm has submitted the major Protocol Amendment having Protocol number "STREAM Stage 2"- V 8.0 dated 13/04/18, Reference File no. CT/48/15 offline on 15-Oct-2018.

Applicant presented their proposal protocol amendment version 8.0 before SEC (Antimicrobial & Antiviral) committees held on 12-12-2018 and 16-01-2019.

SEC Recommendations:

Recommendation of SEC (Antimicrobial & Antiviral) on 12-12-2019: Applicant presented their proposal protocol version 8.0 which is an amendment of previously approved protocol. These amendments have been approved by the respective Ethics committees. During the presentation, the firm also informed that these amendments have already been approved in other countries. Committee after detailed deliberation, recommended as follows:

1. Arm A & D of the study can be removed on the basis of the WHO Aug/2018 guidelines
2. For Amendments of arm C, in which Moxifloxacin by Levofloxacin after 2 years of approval of the trial, adequate justification with supportive evidences should be submitted for review by committee.

Recommendation of SEC (Antimicrobial & Antiviral) on 16-01-2019: In light of recommendation of SEC dated 12-12-2018, the applicant presented their justification. The committee however noted that no justification/evidence were presented in support of changes of the study in which Moxifloxacin is proposed to be replaced by Levofloxacin in the amendment which may make the study irrevelant. Therefore the committee didn't recommend for approval of the amendment.

Now, firm has made request for deliberation in the Technical committee meeting by the applicant. The received version Protocol v.8.0 with due approval from the scientific and ethics committee of the trail sites was submitted to CDSCO for approval. The Subject Expert Committee (SEC) reviewed the amendments and did not approve. The applicant has resubmitted the revised protocol for reconsideration by CDSCO since the revisions are based on the recent evidence and are in line with WHO recommendations ensuring patients safety with the details regarding the revisions and their justification.

- Based on the recent e-vide (Annex 005A WHO guidelines on management of MDR TB published in August 2018) certain revisions have been made in protocol.
- Approval for ver8.0 protocol and related PIS/IFC, other documents has been obtained from different participating sites.
- Applicant has submitted that central as well as site/country level ethics committee and regulatory bodies of all other sites/countries participating in STREAM have approved protocol version 8.0 and these countries have transitioned to the new version of the protocol.

Now, the firm has requested CDSCO to reconsider the revised protocol based on the merits and the rationale of the amendments proposed.

Major changes:

1. Regimen B – Moxifloxacin replaced by Levofloxacin (Risk reduction strategy)

The experience gained in STREAM stage 1 showed that moxifloxacin irrespective of dosage required a rigorous ECG monitoring due to the problem of QTc prolongation, a potential threat to the normal rhythmicity of the heart. This periodic monitoring has been in force throughout the study and would continue even into the current version of protocol v8.0 STREAM Stage 2, AS ECG is a non-invasive procedure, keeping up the highest standard of care.

2. Stopping enrollment to regimen D

In version 8.0 of the protocol, enrolment to regimen D- a six-month regimen with the injectable Kanamycin, will be stopped in view of almost universal agreement among physicians' researchers that elimination of injectable from MDR-TB treatment is now a priority. Several Phase III trials that have already been initiated are investigating only fully-oral regiment is for their efficacy in DR-TB.

Secondary Changes in Protocol Version 8.0

1. Since the start of STREAM Stage 2, all ECSs have been performed in triplicate. With the availability of safety data, this has been modified to single ECGS. For QTcF prolongations of more than or equal to 500ms, two further ECGs will be performed.

2. Laboratory safety teets a previously were performed at each of the visits up to week 132. In version 8.0 central lab tests are required at each visit upt to week 76 only and whenever clinically indicated (36 weeks after treatment completion).

3. PK samples pre and post dose are done only at weeks 2, 12, 24, 40 (weeks 16,20 remove)

4. Inclusion criteria has been changed from sputum smear positive alone to any patient who is either smear positive or GeneXpert positive with a cycle threshold value of 25 or lower could be eligible as this cut off can still pick out culture positive cases.

Information regarding Study at time of Approval:

Primary Objective:

- To assess whether the proportion of patients with a favorable efficacy outcome at week 132 on Regimen b is not inferior to that on Regimen A (WHO approved MDR-TB regimen).
- To compare the proportion of patients who experience grade 3 or greater adverse events, during treatment or follow-up, on Regimen B as compared to Regimen A.

Stage II:

- To assess whether the proportion of patients with a favorable efficacy outcome at week 76 on Regimen C is Superior to that on Regimen B.
- To assess whether the proportion of patients with a favorable efficacy outcome at week 76 on Regimen C is Superior to that on Regimen C is not inferior to that on Regimen B.
- To assess whether the proportion of patients with a favorable efficacy outcome at week 76 on Regimen D is Superior to that on Regimen C is not inferior to that on Regimen B.

Study design:
The STREM study is an international, multi-centre, parallel-group, open-label, randomized, controlled trial.

No. of Centers: 03 site from India.

No. of Subjects in India: Approx 300 subjects enrolled in India for this study

No. of Subjects Globally: Approx1050 subjects enrolled globally in this study

Regulatory status of the drug: The study drug is already approved in India.

Names of participating countries: India, South Africa, Ethiopia Vietnam and Mongolia.

Recommendation of the committee: Applicant presented that enrollment for the study is already over. At present, they have request for approval of amendment relating for follow-up of patients in respect of ECGs, Lab schedule including PK, flexibility on BDQ interruption etc.

After detailed deliberation, the Committee recommended for approval of the proposed amendment.

Agenda No. 2

Proposal of M/s. Excel Life Sciences Pvt. Ltd., in Noida for approval of Clinical trial study protocol no. 010906IN Amendment 1 dated 26-March-2019.

Name of Applicant: M/s. Excel Life Sciences Pvt. Ltd., Noida

Drug Name/indication: (L04AA10) 440 µg DE-109/ Immunosuppressant

Type of Application: Clinical trial study protocol no. 010906IN Amendment 1 dated 26-March-2019.

Phase-III
This is a Phase III study to assess the efficacy and safety of DE-109 440 µg every 2 months in subjects with active, non-infectious uveitis of the posterior segment of the eye (NIU-PS).

Protocol Title: LUMINA: A Phase III, Multicenter, Sham-Controlled, Randomized, Double-Masked Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 µg DE-109 for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye.

Subject: The firm has submitted the application for clinical trial study approval having protocol no. 010906IN dated 26/03/19, Reference File no. CT/55/19 online on 05/07/2019.

Applicant presented their proposal for clinical trial approval before 34th SEC (Ophthalmology) committee held on 06.08.2019 at CDSCO.

SEC Recommendations:

Recommendation of SEC (Ophthalmology) on 06-08-2019: Applicant presented their proposal along with study protocol before the committee. The committee noted that a GCT was conducted earlier with the same drug and same dosage which also had one arm with 1/10 of the therapeutic arm. After detailed deliberation, the committee opined that there is no rationality for conducting the fresh trial with sham arm. Therefore, the committee did not recommend for grant of permission for the conduct of the trial.

Now, firm has made request via e-mail on 11/10/2019 to consider the application for deliberation in the Technical committee meeting.

Rationale for conducting LUMINA study with Sham arm in India:

Firm mentioned that from the start of the SAKURA program in India in November 2011, Santen has committed to make intravitreal sirolimus available to patients in India. However, this will not be possible unless the drug is first approved in the U.S. After an U.S. approval, a Certificate of Pharmaceutical Product (CoPP) can be issued and the drug can subsequently be marketed in India.

Firm also submitted the published literature as annexure for technical committee summary documents.

Information regarding Study at time of deliberation in SEC:

Primary Objective: To evaluate the efficacy of intravitreal injection of 440 µg DE-109 every 2 months as compared with sham for the treatment of active, non-infectious uveitis of the posterior segment of the eye

Study Objectives:

- Secondary (long-term efficacy): A secondary objective of this study is to evaluate the long-term efficacy (> 6 months and up to one year) of intravitreal injection of 440 µg DE-109 every 2 months for the treatment of active, non-infectious uveitis of the posterior segment of the eye
- Secondary (safety): A secondary objective of this study is to evaluate the safety of intravitreal injection of 440 µg DE-109 every 2 months for up to one year of dosing for the treatment of active, non-infectious uveitis of the posterior segment of the eye.

Study design:
The 12-month study consists of a 6-month, randomized, double-masked, parallel design, sham controlled evaluation of DE-109 440 µg every 2 months followed by a 6-month, open-label period in which all subjects will receive DE-109 440 µg every 2 months.

No. of Centers: 11 Investigator sites from India.

Study Duration: 2 years

No. of Subjects in India: Approx 75 subjects enrolled in India for this study

No. of Subjects Globally: Approx 200 subjects enrolled globally in this study

Regulatory status of the drug: The study drug is already approved in United States

Names of participating countries: India, Italy, Spain and United States of America.

Recommendation of the committee: After detailed deliberation, the committee recommended for grant of permission to conduct the proposed global clinical trial.

Agenda No. 3

Proposal of M/S Synokem Pharmaceuticals Limited for grant of manufacturing and marketing permission of FDC of Teneligliptin 20mg/20mg + Pioglitazone 15mg/30mg Tablets .

Applicant: M/s Synokem Pharmaceuticals Limited

Drug name: Fixed dose combination of Teneligliptin 20mg/20mg + Pioglitazone 15mg/30mg

Type of Application: Manufacturing and Marketing

Proposed Indication: In the treatment of type 2 diabetes mellitus.

Regulatory Status: As stated by firm, this FDC is not yet approved in any country.

The proposal was placed before 53rd SEC (Endocrinology & Metabolism) in its meeting held on 19.02.2019

Recommendations of 53rd SEC (Endocrinology & Metabolism) meeting held on 19.02.2019:

The firm presented the Bioequivalence study results along with protocol for Clinical Trial. The Committee observed that abnormal laboratory values in respect of Hb, PCV, RBC, WBC and Platelets in one subject enrolled in the bioequivalence study were inconsistent with each other. Therefore the committee recommended that the firm should submit raw data of all the subjects along with accreditation/approval status of the bio analytical lab used for BE study for the review by the committee. The committee also opined that the CT protocol presented is highly inadequate in terms of objectives, inclusion/exclusion criteria, discontinuation /rescue criteria etc.

On subsequent response of the applicant, the proposal was again deliberated in 55th SEC (Endocrinology & Metabolism) meeting held on 21.05.2019.

Recommendations of 55th SEC (Endocrinology & Metabolism) meeting held on 21.05.2019:

In light of the earlier recommendations of the committee dated 19.02.2019, the firm presented the raw data. The committee noted that there is a gross inconsistency in the laboratory results of patient no. 1 compromising the reliability of the data of the study. Therefore the committee recommended to repeat the bioequivalence study with the already approved protocol.

However, the firm did not agree with the recommendations of SEC and has requested to deliberate the proposal in Technical Committee for considering the application. Accordingly the proposal was placed before 46th Technical Committee meeting held on 01.07.2019.

Recommendations of 46th Technical Committee meeting held on 01.07.2019:

The committee, after detailed deliberation, recommended that, CDSCO shall conduct inspection at the BA-BE study centre to verify the raw data, changes of the researchers, if any, during the conduct of the study at the site etc. for further consideration.

As per the recommendations of 46th Technical Committee meeting held on 01.07.2019, the inspection was carried out from 05.09.2019 to 06.09.2019 at BE study centre i.e. M/s. Notrox Research Private Limited, Salem, Tamilnadu. Further, compliance verification was carried out on 02.01.2020 and inspection team has observed that abnormal increase of the blood test value for Subject no.1 was only due to the procedural errors and Subject no.1 was not affected by the study.

Recommendation of the Committee: After detailed deliberation, the committee noted that the inspection team has observed that abnormal increase of the blood test value for Subject no.1 was due to the procedural errors and recommended that the firm should submit Phase III clinical trial protocol containing details as recommended earlier by the SEC including details of cardiac monitoring through ECG/ ECHO and rationality of the dose etc. for review by the SEC.

Agenda No. 4

Proposal of M/S Entod pharmaceuticals ltd., for grant of manufacturing and marketing permission of FDC of Tropicamide IP 0.2mg + Phenylephrine Hydrochloride IP 3.1mg + Lidocaine Hydrochloride IP 10mg per ml Injection

Applicant: M/S Entod pharmaceuticals ltd

Drug name: Tropicamide IP 0.2mg + Phenylephrine Hydrochloride IP 3.1mg + Lidocaine Hydrochloride IP 10mg per ml Injection

Type of Application: Manufacturing and Marketing

Proposed Indication: It is proposed to be indicated for cataract surgery to obtain mydriasis and intraocular anesthesia during the surgical procedure

Regulatory Status: Firm has claimed that FDC was already approved and being marketed since July 2015 in the following countries with different brand names i.e., Fydrane; Mydane; Mydrane; Mydricaine

Marketed countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Greece, Finland, France, Croatia, Iceland, Italy, Luxembourg, The Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic, United Kingdom"

Recommendations of 29th SEC (Ophthalmology) held on 30.10.2018;

The committee recommended that the firm should make detailed presentation on clinical as well as non-clinical data to consider the matter further.

Also the firm should submit protocol for conducting Phase III clinical trial in Indian population".

On subsequent response of the applicant, the proposal was again deliberated in 31st SEC (Ophthalmology) held on 07.02.2019.

Recommendations of 31st SEC (Ophthalmology) held on 07.02.2019:

"The firm didn't present any additional information/data for seeking clinical trial waiver. In respect of the ocular toxicity data on rabbit and rats presented, the committee recommended that the firm should submit the raw data with reference to cornea and anterior chamber. The firm should also submit Phase III clinical trial protocol for review by the committee".

On subsequent response from the applicant, the proposal was placed in 32nd SEC (Ophthalmology) meeting held on 15.04.2019.

Recommendations of 32nd SEC (Ophthalmology) meeting held on 15.04.2019:

"In light of the earlier recommendation, the firm presented raw data only with reference to cornea. After detailed deliberation, committee recommended that firm should generate preclinical data with reference to anterior chamber also including endothelial cell density. This study has to be followed by Phase III clinical trial as recommended earlier by the committee."

On subsequent response from the applicant, the proposal was placed in 33rd SEC (Ophthalmology) meeting held on 06.06.2019.

Recommendations of 33rd SEC (Ophthalmology) meeting held on 06.06.2019:

"Firm presented their proposal before the committee. After detailed deliberation, committee observed that firm presented only the data with respect to corneal thickness however endothelial cell density was not studied which was asked by the committee earlier. Hence the firm should generate data with respect to endothelial cell density. Further the firm should also submit Phase III clinical trial protocol. "

On subsequent response from the applicant, the proposal was placed in 34th SEC meeting held on 06.08.2019.

Recommendations of 34th SEC (Ophthalmology) meeting held on 06.08.2019:

"In light of recommendation of the SEC dated 06.06.2019, firm presented the endothelial cell density data. The firm requested the committee for waiver of Phase III Clinical trial on the basis that the similar product (Mydrane) is approved in UK and other countries. The committee noted that tropicamide for intracameral route has not been approved in India. After detailed deliberation, the committee recommended that the firm should conduct Phase III clinical trial, Accordingly firm should submit Clinical trial protocol to the CDSCO for review by the committee. "

However, the firm did not agree with the recommendations of Subject Expert Committee and the firm submitted scientific summary to deliberate the proposal in Technical Committee for Phase III CT waiver.

Recommendation of the committee: After detailed deliberation, the committee recommended for grant of permission to manufacture and market the proposed FDC subject to condition that the firm should conduct Phase IV clinical trial for which the protocol should be submitted for review by the SEC. The results of first 25 patients from the Phase IV trial should be submitted for considering continuation of the manufacturing permission.

Agenda No. 5

Proposal of M/s Novartis Healthcare Private Limited for grant of manufacturing and marketing permission of FDC of Vildagliptin 50mg + Metformin 850mg + Glimepiride 2mg Tablets

Applicant: M/S Novartis healthcare Private Limited

Drug name: Fixed dose combination of Vildagliptin 50mg + Metformin 850mg + Glimepiride 2mg Tablets

Type of Application: Manufacturing and Marketing

Proposed Indication: As an adjunct to diet and exercise in patients inadequately controlled with Metformin and sulfonylurea.

Regulatory Status: As stated by firm, this FDC is not yet approved in any country.

Recommendations of SEC (Endocrinology & Metabolism) held on 28.08.2018:

The committee opined that there is no rationality in combining two insulin secretagogues in one FDC. Moreover, the committee also noted that the clinical study data presented by the firm is not on the proposed FDC. Further the firm informed the committee that proposed FDC is not marketed anywhere in the world. Hence, the committee did not recommend for the proposed FDC.

On subsequent response of the applicant, the proposal was again deliberated in SEC (Endocrinology & Metabolism) held on 11.12.2018.

Recommendations of SEC (Endocrinology & Metabolism) held on 11.12.2018:

The committee opined that although SU & DPP-IV inhibitors act differently, the outcome of both the drugs is to stimulate insulin secretion. The justification that this FDC will be useful for patients who require 3 drugs as add-on therapy and hence FDC of the 3 drugs will be useful was not justified with adequate data. The clinical trial data presented is on the 3 drugs given as add-on therapy and not with the proposed FDC. The committee also noted that the proposed FDC is not approved in any country. In view of above, committee after detailed deliberation reiterated its earlier stand and didn't recommend approval of the proposed FDC.

On subsequent response from the applicant, the proposal was placed in 46th Technical Committee meeting held on 01.07.2019.

Recommendations of 46th Technical Committee meeting held on 01.07.2019:

The committee, after detailed deliberation, agreed with the recommendation of the Subject Expert Committee (Endocrinology & Metabolism) dated 11.12.2018 and didn't recommend for approval for the FDC.

However, the firm submitted scientific summary to re-deliberate the proposal in the Technical Committee.

Recommendation of the committee: After detailed deliberation, the committee recommended that proposed prescribing information with detailed information in respect of specific conditions, indication, dosage etc. for which the FDC is intended to be used supported by justification/rationality along with risk management plan for the proposed FDC for further review by the Technical Committee.

Agenda No. 6

Proposal of M/s Akums Drugs & Pharmaceuticals Ltd., for grant of manufacturing and marketing permission of FDC of Dextromethorphan Hydrobromide IP 10mg + Phenylephrine HCl 5mg + Chlorpheniramine maleate 2mg film coated tablet with indication for relief from the symptoms of common cold and nasal congestion and associated fever due to allergic reactions.

Applicant: M/s Akums Drugs & Pharmaceuticals Ltd.

Drug name: FDC of Dextromethorphan Hydrobromide IP 10mg + Phenylephrine HCl 5mg + Chlorpheniramine maleate 2mg film coated tablet

Type of Application: Manufacturing and Marketing.

Proposed Indication: It is proposed to be indicated for relief from the symptoms of common cold and nasal congestion and associated fever due to allergic reactions.

Regulatory Status: As stated by firm, this FDC is not yet approved in any country.

Recommendations of 38th SEC (Pulmonary) held on 29.05.2019:

"The firm made a detailed presentation before the committee. The committee noted that the proposed FDC has already been allowed for continued marketing in various dosage forms viz soft gelatin capsule, dispersible tablets as well as syrup. Hence the committee didn't recommend for approval of proposed additional dosage form of the same FDC."

However, the firm did not agree with the recommendations of Subject Expert Committee and requested to place the proposal in Technical Committee for deliberation.

Recommendation of the committee: After detailed deliberation, the committee recommended that the firm should conduct a BE study for the proposed FDC for which protocol should be submitted for review by the SEC.

Agenda No. 7

Proposal of M/s Synokem Pharmaceuticals Ltd., for grant of manufacturing and marketing permission of FDC of Pregablin IP 75mg (PR) + Mecobalamin IP 1500mcg+ Nortryptyline HCl 10mg film coated bilayered tablet with indication for the treatment of patients with diabetic peripheral neuropathic pain with coexistent Vitamin B12 deficiency

Applicant: M/s Synokem Pharmaceuticals Ltd.

Drug name: Pregabalin IP 75mg (PR) + Mecobalamin IP 1500mcg + Nortryptyline HCl 10mg film coated bilayered tablet.

Type of Application: Manufacturing and Marketing.

Proposed Indication: It is proposed to be indicated for the treatment of patients with diabetic peripheral neuropathic pain with coexistent Vitamin B12 deficiency.

Regulatory Status: As stated by firm, this FDC is not yet approved in any country.

Recommendations of 45th SEC (Neurology & Psychiatry) held on 13.03.2019:

"Committee however observed that no justification for combination of the 3 drugs was presented. Hence the committee didn't recommend for approval of the FDC."

On subsequent response of the applicant, the proposal was again deliberated in 51st SEC (Neurology & Psychiatry) held on 05.09.2019.

Recommendations of 51st SEC (Neurology & Psychiatry) held on held on 05.09.2019:

"After detailed deliberation the committee reiterated its earlier recommendation dated 13.03.2019".

However, the firm did not agree with the recommendations of Subject Expert Committee and requested to place this proposal in Technical Committee for deliberation.

Recommendation of the committee: After detailed deliberation, the Committee recommended that the firm should conduct Phase III clinical trial in specific indication for which the FDC is justified and intended to be used for review by the SEC.

Agenda No. 8

Proposal of M/s Novartis Pharmaceuticals Ltd. for Import and Marketing of Nepafenac Ophthalmic Suspension 0.3% w/v (additional indication) with request for waiver of local clinical trial.

Applicant:- M/s Novartis Pharmaceuticals Ltd.

Drug Name:- Nepafenac Ophthalmic Suspension 0.3% w/v

Type of Application:- Permission for Import and Marketing of Nepafenac Ophthalmic Suspension 0.3% w/v (additional indication)

Proposed Additional Indication:

1. Reduction in the risk of postoperative macular edema associated with cataract surgery in diabetic patients.
2. Prevention and treatment of post-operative pain and inflammation associated with cataract surgery.

CDSCO approval status:-

1. Nepafenac Ophthalmic Suspension 0.3%w/v (Additional Indication) is approved on 09.11.2018, indicated for the treatment of post-operative pain and inflammation associated with cataract surgery to M/s Novartis Pharmaceuticals Ltd.
2. Nepafenac Ophthalmic Suspension 0.3% w/v is approved on 13.07.2018 Indicated for the treatment of pain and inflammation associated with cataract surgery to M/s Ajanta Pharma Ltd.
3. This directorate has approved Nepafenac Ophthalmic suspension 0.1%w/v (1mg/ml) on 31.03.2008 indicated for the treatment of pain and inflammation associated with cataract surgery.

International approval status:

S. No.	Approval Country	Strength	Approved Therapeutic Indication
1	US	Ophthalmic suspension 0.1% (1mg/ml)	NEVANAC ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery
2	US	Ophthalmic suspension 0.3% (3mg/ml)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.
3	UK	Ophthalmic suspension 0.1% (1mg/ml)	1. to prevent and relieve eye pain and inflammation following cataract surgery on the eye 2. To reduce the risk of macular edema (swelling in the back of the eye) following cataract surgery on the eye in diabetic patients.
4	UK	Ophthalmic suspension 0.3% (3mg/ml)	1. To prevent and relieve eye pain and inflammation following cataract surgery on the eye. 2. To reduce the risk of macular edema (swelling in the back of the eye) following cataract surgery on the eye in diabetic patients.

SEC Recommendation:-

Recommendation of SEC (Ophthalmology) meeting held on 13.03.2018:- The firm presented their proposal for additional strength and additional indication of Nepafenac ophthalmic suspension 0.3% w/v before the committee and requested for clinical trial waiver.

After detailed deliberation, the committee recommended that the firm should conduct the clinical trial to generate the safety and efficacy data in Indian patients for the proposed indication. Accordingly, protocol should be submitted for review by the committee.

Recommendation of SEC (Ophthalmology) meeting held on 16.08.2018:- The firm presented their proposal for Nepafenac ophthalmic suspension 0.3% w/v before the committee for two indications

1. Prevention and treatment of postoperative pain and inflammation associated with cataract surgery.
2. Reduction in the risk of postoperative macular edema associated with cataract surgery in diabetic patients.

The Nepafenac ophthalmic suspension 0.3% w/v is already approved for treatment of postoperative pain and inflammation associated with cataract surgery. After detailed deliberation, the committee recommended for grant of permission to market Nepafenac ophthalmic suspension 0.3% w/v for prevention and treatment of postoperative pain and inflammation associated with cataract surgery. As regards the other indication the committee opined that there is therapy available for diabetic macular edema. Therefore, the committee recommended that the firm should conduct Phase III clinical trial for the same indication.

Firm has appealed for re-deliberation in the next Technical Committee Meeting for Nepafenac Ophthalmic Suspension 0.3% w/v for reduction in risk of postoperative macular edema associated with cataract surgery in diabetic patients and submitted their justification that the additional indication for which Permission for Import and Marketing of Nepafenac Ophthalmic Suspension 0.3% w/v they had applied is already approved in more than 40 countries globally including ICH/Major markets.

Further, the firm had given following justification for the proposal:

i. No drug/therapy is currently approved in India for reduction in the risk of post-operative macular edema following cataract surgery in diabetic patient (unmet need).
ii. There is high disease burden of macular edema in diabetic patients undergoing cataract surgery.

iii. Patients population is exactly similar to the already approved indication for the formulation i.e. in patients undergoing cataract surgery where it is already approved to control pain and inflammation. This should essentially be considered as additional claim for an already approved indication.

iv. Efficacy & Safety data of Nepafenac 0.3%

— Nepafenac 0.3% has proven efficacy & safety in preventing macular edema as seen in various published studies conducted in 3000+ patients across the world.

— Latest PSUR does not indicate any major safety concerns & the safety profile of Nepafenac 0.3% is comparable to Nepafenac 0.1% w/v

— Nepafenac does not perform differently in Indian patients compared to the overall population, suggesting the lack of ethnic difference (based on the already approved indication).

Recommendation of the committee: After detailed deliberation, the committee recommended for grant of permission to market the product for the proposed additional indication.

Agenda No. 9

Proposal of M/s Abbott Healthcare Ltd. for Manufacturing and Marketing of Triamcinolone Tablets 16mg (Additional Strength)

Applicant:- Abbott Healthcare Ltd.

Drug Name:- Triamcinolone Tablet 16mg

Type of Application:- Manufacturing and Marketing

Proposed Indication: for Adrenal insufficiency, Allergy rhinitis (seasonal or perennial), Asthma, Carditis (Acute), rheumatic disorder of endocrine system, disorder of eye, disorder of Gastrointestinal tract, disorder of endocrine system, disorder of eye, disorder of hematopoietic structure, disorder of respiratory system, disorder of skin, Drug allergy, Exacerbation of multiple sclerosis (Acute), Inflammatory disorder of musculoskeletal system, Neoplastic disease Nephrotic syndrome, idiopathic or lupus erythematous-included, systemic lupus erythematous, transfusion reaction due to serum protein reaction, Trichinosis, with neurologic or myocardial involvement, Tuberculosis of meninges (adjunct).

CDSCO approval status:- Triamcinolone Tablet 16mg is not approved (Triamcinolone Tablets 2mg, 4mg and 8mg are official in IP 2010)

International approval status:- Triamcinolone Tablets 16mg is not approved anywhere in the world.

SEC Recommendation:-

Recommendation of 54th SEC (Endocrinology & Metabolism) meeting held on 23.04.2019

The firm presented their proposal for the higher strength of Triamcinolone tablet 16mg. The committee however noted that this strength is not marketed in any country & in fact had been discontinued from USA. However reasons for discontinuation are not clear. After detailed deliberation, the committee recommended that the firm should submit the rationality for the higher strength with supportive literature as well as the reason of discontinuation from USA.

Recommendations of 61st SEC (Endocrinology & Metabolism) meeting held on 20.11.2019

The firm presented the clarification in light of earlier recommendation of the SEC meeting held on 23/04/2019. After detailed deliberation, the committee reiterated the earlier SEC recommendation.

Firm has requested to deliberate their proposal in the Technical Committee.

Recommendation of the committee: After detailed deliberation, the committee recommended that firm should submit the detailed information regarding the present regulatory status, use, indication etc. of Triamcinolone 16mg Tablet in USA. The CDSCO may also obtain the regulatory status and other related details on use of Triamcinolone 16mg Tablet in present context from US-FDA for further review by the Technical Committee.

Agenda No. 10

Proposal is of M/s GlaxoSmithKline Pharmaceuticals Limited, Mumbai for the grant of Permission for the import of Inactivated Influenza Vaccine (Split Virion) IP Quadrivalent, [Brand name: Fluarix-Tetra] in Form CT-20 from M/s GSK Biologicals Branch of SmithKline Beecham Pharma GmbH & Co.KG Zirkusstraße 4001069 Dresden, Germany with indication for active immunization of adults and children above 36 months of age without conduct of clinical trial in India. (Application ref. no. BIO/IMP/19/000018)

Applicant: M/s GlaxoSmithKline Pharmaceuticals Limited, Mumbai

Drug Name: Inactivated Influenza Vaccine (Split Virion) IP (Quadrivalent)

Type of application: Market authorization in Form CT-20 for import of Inactivated Influenza Vaccine (Split Virion) IP Quadrivalent with indication for active immunization of adults and children from 36 months of age without conduct of clinical trial in India.

CDSCO approval status: Earlier based on the recommendation of SEC dated 03.10.2018 and based on India specific study result, CDSCO had granted Marketing Authorization in Form 45 vide permission no. IMP/BIO/19/000003 dated 04.04.2019 for Inactivated Influenza Vaccine (Split Virion) IP [Brand name: Fluarix-Tetra] Quadrivalent for the indication of children from 6 to 35 months age group.

International approval status: United States, Australia, United Kingdom

SEC (Vaccine) Recommendations:

SEC meeting	Recommendations
SEC Vaccine meeting dated 21.10.2019 (re-deliberation)	• The firm made presentation for waiver of Phase III & IV local clinical trials for age group greater than 35 months. • The committee noted that there is no data on the vaccine of the firm in the proposed age group in the country. Further, there are other approved brands already available for the same indication. • After detailed deliberation the committee did not recommend for waiver of local clinical trial.
SEC Vaccine meeting dated 14.05.2019	• The firm presented the proposal for waiver of clinical trial requirement for extension of the indication to higher age groups. After detailed deliberation, the committee recommended that the firm should conduct Phase III local clinical trial in the proposed age groups.

Now, firm has made request for reconsideration of proposal for Technical Committee meeting for grant of Market Authorization of Inactivated Influenza vaccine IP (Split Virion) Quadrivalent with indication for active immunisation of adults and children from 36 months of age without conduct of clinical trial in India.

Firm has given following rationality/justification for clinical trial waiver for Trivalent Inactivated Influenza vaccine (Split Virion) as follows:

- Trivalent Influenza Vaccine [Brand name: Fluarix] is approved for marketing in India since 2003.
- The efficacy, immunogenicity, safety profile of GSK's FLU-D-QIV in South Asian subgroup (India and Bangladesh) which comprised of 25% of the overall population recruited in the Global Clinical Trial (FLU D-QIV-004 in children 6-35 months of age) was comparable to the overall study results.
- Immunogenicity, and safety of GSK's Flu Q-QIV in South Asian (Bangladesh) children 3-8 years of age in global clinical trial FLU Q-QIV-006 provide supportive evidence (via an immunogenicity bridge approach between D-QIV and Q-QIV) for the administration of D-QIV in Indian children >3 years of age.
- These available results from the D-QIV-004 and Q-QIV-006 study can be extrapolated to Indian population of age above 35 months (3 years).

1. Synopsis of study D-QIV-004

Phase: Phase III

Age group: Children 6 to 35 months of age:

Phase III randomized, multi-country, non-influenza vaccine comparator-controlled study to demonstrate efficacy of Flu D-QIV in children 6 through 35 months of age. Total 465 subjects from India participated in the study. Whereas 2911 children participated in D-QIV-004 study from Bangladesh, which constituted approximately 24% of total subjects in the study. Since overall safety and immunogenicity of D-QIV in subjects from India and Bangladesh found to be similar to the rest of the study participants from other countries, GSK propose to extrapolate this data to the population above 35 months of age.

This study was conducted by 3 principal investigators in India.

- Dr. Ashish Bavdekar, K.E.M Hospital, Department of Pediatrics, Sardar Moodliar Road, Pune, 411 011, India.
- Dr. Shashi Kant All India Institute of Medical Sciences, Community Medicine, Ballabgarh, Faridabad, 121004, India.
- Dr. Sanjay Lalwani Bharatiya Vidyapeeth Deemed University Hospital, Pune Satara Road, Kataraj, Dhankawadi, Pune, India.

Conclusions on efficacy and immunogenicity:

Results of the primary efficacy study demonstrate that:

- Vaccine efficacy (VE) of FLU D-QIV in the prevention of RT-PCR confirmed moderate to severe influenza A and/or B disease due to any seasonal strain in comparison to non-influenza vaccine controls in children 6 to 35 months was 54.1% (97.5% CI: -32.7% to 86.4%).

- VE of FLU D-QIV in the prevention of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal strain, when compared to non-influenza vaccine controls in children 6 to 35 months was 43.4% (97.5% CI: -4.1% to 70.2%).

2. Synopsis of study Q-QIV-006 (Phase III)

Phase: Phase III

Subjects: Male or female children 3 to 8 years of age (inclusive) at the time of first vaccination. Total 1000 children (500 in Q-QIV arm of which 479 completed study) participated from Bangladesh. (Similar ethnicity with Indian population)
Multi-center study conducted at 15 centres across Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, and Turkey.

Further firm has submitted that, following phase III pivotal clinical studies were conducted outside the country which support the indication as proposed in the Indian Prescribing Information (PI) in children and adults age group:-

Study D-QIV-001: Immunological non-inferiority study of D-QIV versus Fluarix for the three common strains and superiority of the additional B-strain contained in D-QIV in adults 18 years of age and above.

Study D-QIV-003: Immunological non-inferiority study of D-QIV versus Fluarix for the three common strains and superiority of the additional B-strain contained in D-QIV in children 3 through 17 years of age. This study also included description of immunogenicity and safety of D-QIV in children aged 6 to 35 months.

Study D-QIV-008: Immunological non-inferiority study of D-QIV versus Fluarix for the three common strains and superiority of the additional B-strain contained in D-QIV, and lot-to-lot consistency study of three manufacturing lots of D-QIV in adults aged 18 years and above.

Firm has submitted executive summary of above mentioned clinical trials in support of the proposed expansion of indication from "6 to 36 months" to "Adults and children from 36 months of age group" without conduct of clinical trial in India. Further, detailed clinical trial reports of said clinical trials as per the New Drugs & Clinical Trials Rules, 2019 has not been submitted.

Recommendation of the committee: After detailed deliberation, the committee recommended for grant of permission to import and market the vaccine in the proposed age groups.

Agenda No. 11

Proposal is of M/s Zuventus Healthcare Ltd., Mumbai for grant of market authorization in Form 45 for Trivalent Inactivated Influenza vaccine (Split Virion) to be imported from M/s Hualan Biological Bacterin Co. Ltd. Jia No.1-1, Hualan Ave., Xinxiang, Henan, China, Zip Code: 453003 without conduct of clinical trial in India.

Applicant: M/s Zuventus Healthcare Ltd., Mumbai

Drug Name: Trivalent Inactivated Influenza vaccine (Split Virion) [Single dose in Pre filled syringe for 0.25ml (Pediatric dose) & 0.5ml (Adult dose)]

Type of application: Market authorization in Form 45 for import of Trivalent Inactivated Influenza vaccine (Split Virion) without conduct of clinical trial in India.

Proposed Indication: For active immunization against influenza disease caused by influenza virus subtypes A and B contained in the vaccine for prophylaxis of the influenza caused by the contained vaccine strain.

CDSCO approval status: The vaccine manufactured by M/s Hualan Biological Bacterin Co., Ltd. China is not approved by CDSCO.

International approval status: The vaccine is approved in China.

SEC (Vaccine) Recommendation dated 18.03.2019: In light of recommendation of the SEC meeting held on 18.03.2019, the firm presented the safety and efficacy data generated in China for grant of Market Authorization with phase III clinical trial waiver. After detailed deliberation, the committee recommended that the firm should conduct Phase III clinical trial and protocol etc. may be submitted for evaluation.

Further, firm had made request for reconsideration of the proposal for Technical Committee meeting for grant of Market Authorization of Trivalent Inactivated Influenza vaccine (Split Virion) without conduct of clinical trial in India. In this regard, firm has given following rationality/justification for clinical trial waiver for Trivalent Inactivated Influenza vaccine (Split Virion) as follows:

- Inactivated Influenza vaccine (Split Virion) is a WHO pre-qualified vaccine and WHO prequalification assures the vaccine procured by UNICEF and GAVI meets the highest international quality standards and conducting Clinical trial may not yield any additional information and granting a waiver can help to bring the vaccine in the country immediately.

- Due to shortage of the vaccine, the department of Pharmaceuticals vide letter dated 14.02.2019 had directed to all the importers/manufacturers to submit a report on product, sale and stock position of the flu vaccines/tablet/inhalation to Government.

- It was mentioned that India is currently facing shortage in Trivalent Vaccine and stated that this case if approved by the Technical Committee can be qualified for consideration of Clinical trial waiver; as it pertains to National emergency/extremely emergency category, Firm submitted news articles on prevalence report on Flu out breaks/other reports for consideration.

Earlier, firm had submitted the clinical trial reports of Inactivated Influenza vaccine (split virus) conducted in China as below:

- Phase III clinical trial (single centre, randomized, double-blind and parallel Control) Paediatric Inactivated Influenza vaccine (split virus) in 6 months 36 months age group (2doses 4 weeks apart): A total of 769 people (including 514 in test group, 255 in control group) of the Paediatrics influenza vaccine by comparing with VAXIGRIP of M/s Shenzhen Aventis Pasteur Biological Products Co., Ltd. Conducted in 2006 at Jintan City, Jiangsu province. The clinical trial results indicated that the antibody seroconversion rate of H1N1, H3N2, and B were 93.58%, 88.72%, and 81.32%; with GMT increase of 51.1, 20.9, and 15.7 respectively. It has been reported that there were expected adverse reaction in test group and control group are 22.59% and 22.96% respectively.
- Another Phase III clinical trial in adults (16-60 years age), children (6 to 12 years age), and infants (6 months to 3 years age) age group: 60 subjects were included in the first stage and divided into three age groups, 20 subjects for each age group. A total of 840 subjects were included in the second stage and divided into four age groups, 360 subjects in the elderly and infant groups (240 subjects in test group and 120 in the control group); 480 subjects were included up in the adult and children groups (320 subjects in the test group and 160 in the control group). The eligible subjects were randomly divided into the test group and the control group in proportion of 2:1. The results of this phase III Clinical trial is as below:

  Safety results: There was no statistically significant difference in cases and incidence of adverse reactions in each age group of the test and Control groups; and there was also no statistically significant difference in severity distribution between the two groups. It showed that the influenza vaccine of Hualan Bio had a good safety compared with the control vaccine. There were 4 cases of serious adverse reactions in the test group and 1 case in the Control group. Cases and incidence of systemic and local reactions of the test vaccine were higher than those of the Control group, but there was no statistically significant difference.

Immunogenicity results: The results of the clinical trial showed that: after administering the test vaccine, the antibody seroconversion ratios (4-fold increase) of different subtypes of each age group were higher than 80%, far exceeding the European specification (40%); the positive rates (the proportion of subjects with HI antibody GMT≥1:40 after immunization) of different subtypes of each age group were high, exceeding the highest European specification (70%).The antibody GMT of all different subtypes of each age group after immunization increased, especially subtype H1N1 and subtype B. The subtype H3N2 antibody was at a higher level before immunization, so the increase after immunization was limited. With the age increase, the increase of antibody after immunization became slow. The immunogenicity results showed that the influenza vaccine of Hualan Bio had a good immunogenicity performance in the proportion of subjects with the seroconversion ratios and HI antibody GMT ≥ 1:40 after vaccination in each age group, especially the elderly and infant groups. It was concluded that the influenza vaccine of Hualan Bio is safe and immunogenic in the age group of 6 months of age and over.

The subject proposal was discussed in Technical Committee meeting held on 01.07.2019 wherein after detailed deliberation, the committee recommended that to obtain opinion from ICMR and Dr. Lalit Dar, Professor, Department of Microbiology, Head, Virology Section, AIIMS, New Delhi and place the opinions before the Technical Committee for further consideration.

Accordingly, this office had forwarded the proposal to DG, ICMR and Dr. Lalit Dar, AIIMS, New Delhi on 05.08.2019.

Now, opinion of both the experts has been received as "*DCGI may follow the same precedence as followed earlier for according approval for Influenza vaccines based on absence of clinical trial data from India*" in the matter.

As per records, this office has not granted approval for Influenza vaccines based on absence of clinical trial data from India.

Recommendation of the committee: After detailed deliberation, the committee recommended that the firm should conduct Phase III clinical trial for which protocol should be submitted for review by the SEC.

Agenda No. 12

Proposal of Wavier for Phase IV Clinical Trial for Inotuzumab Ozogamicin powder for concentrate for solution for infusion - 1mg

Applicant: - M/s. Pfizer Products India Private Limited, India

Drug Name: - Inotuzumab Ozogamicin powder for concentrate for solution for infusion - 1mg

Type of Application: - Wavier for Phase IV Clinical Trial

Proposed Indication: Indicated as monotherapy for the treatment of adults with relapsed or refractory CD22- positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).

CDSCO approval status: - Approved on 10-Oct-2018. (Permission No. IMP/BIO/18/000023)

International approval status: -
The marketing authorization holder (MAH) received first regulatory approval on 29th June 2017 in the European Union (EU). The drug is currently approved for marketing in 51 countries including United States (US), Japan, and Switzerland, United Kingdom, Australia, Canada.

Orphan Drug status:
Inotuzumab Ozogamicin has been granted Orphan Drug status in 7 countries including European Union (EU), United States (US), Australia, Japan, Russia, South Korea and Switzerland

Breakthrough Therapy Designation (BTD) and Priority Review (PR)
The US Food and Drug Administration (FDA) granted BTD and Priority Review to Inotuzumab Ozogamicin on 15 October 2015.

SEC Recommendation: -

1. SEC meeting on 20.Jun. 2018: The firm presented their proposal before the committee. The committee noted that the drug has been granted Orphan drug status in USA and EU. After detailed deliberation, the committee recommended for grant of permission to import and marketing the drug for the proposed indication subject to the condition that the firm is required to conduct the Phase IV clinical trial in at least 50 patients. Accordingly, the firm should submit the

protocol within 3 months from date of issue of permission and submit the results within 2 years.

2. SEC meeting on 16.Jul.2019: The firm presented their request for waiver of Phase IV clinical trial. After detailed deliberation, the committee however did not agree for waiver of Phase IV clinical trial. The committee reiterated that as per earlier condition the firm should complete the study within the timelines of 2 years of approval of the drug otherwise, it should be viewed as non-compliance to the conditions of the permission.

Firm has requested for wavier of Phase IV Clinical Trial and provided justification that as per ICMR, projected cases of lymphoid leukemia in India in 2020 is 27,709 hence, relapsed/refractory adult ALL cases will be lower than this. Inotuzumab ozogamicin is indicated for the treatment of relapses/refractory adult ALL patients so it falls under the definition of "orphan drug" means a drug intended to treat a condition which affects not more than five lakh persons in India as per "*New Drugs and Clinical Trials Rules, 2019*" effective from 19th March 2019. Inotuzumab Ozogamicin has been granted Orphan Drug status in 7 countries including European Union (EU), United States (US), Australia, Japan, Russia, South Korea and Switzerland.

In light of "*New Drugs and Clinical Trials Rules, 2019*" effective from 19th march 2019, under the regulatory provisions of Chapter X (Import or manufacture of new drug for sale or for distribution), under point 75 (Application for permission to import new drug for sale or distribution)- point 7, sub point (iv), stating- 'Provided that the Central Licensing Authority may relax this condition, 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'

Further as per provision of Fifth schedule of the said regulation on post market assessment of the said rules, we are proposing the following measures on active surveillance to generate additional safety data for the product:

- Active surveillance to submit safety data from the first 50 patients treated with Inotuzumab ozogamicin, post marketing
- Submission of regular periodic safety update (PSUR) reports for the extended period of four years
- Participation in global Phase 4 study in approved indication

Recommendation of the committee: After detailed deliberation, the committee agreed for waiver of the Phase IV clinical trial and the condition requiring Phase IV clinical trial should be deleted from the new drug permission.

Agenda No: 13

Proposal of M/s Gurmail Brothers for grant of Import& Marketing permission of Midodrine hydrochloride tablets 2.5mg (additional Indication) with request for waiver of local clinical trial.

Applicant:-M/s. Gurmail Brothers

Drug Name: Midodrine hydrochloride tablets 2.5mg (additional Indication)

Type of Application: Permission for Import& Marketing of Midodrine hydrochloride tablets 2.5mg (additional Indication)

Proposed Additional Indication:

Management of Refractory Ascites

CDSCO approval status

Drug Name	Indication	Date of Approval
Midodrine Hydrochloride Tablets 2.5 mg	For the treatment of symptomatic orthostatic hypotension.	02.09.2016
Midodrine Hydrochloride Tablets5/10 mg	For the treatment of symptomatic orthostatic hypotension.	20.02.2019

International approval status:

Drug Name	Regulatory Status	Approval/ Withdrawal Date	Country	Approved Indications
Midodrine Hcl Tablets USP 2.5mg, 5mg & 10mg	Approved	10-Sep-2003	United States	In treatment of Orthostatic Hypotension
Midodrine Hcl Tablets USP 2.5mg, 5mg & 10mg	Approved	16-Dec-2015	Austria	In treatment of Orthostatic Hypotension
Midodrine Hcl Tablets USP 2.5mg, 5mg & 10mg	Approved	12-Apr-2006	Canada	In treatment of Orthostatic Hypotension

Midodrine Hcl Tablets USP 2.5mg, 5mg & 10mg	Approved	18-Mat-2015	Denmark, Finland, Netherlands, Sweden	In treatment of Orthostatic Hypotension

Note:-Proposed additional Indication "Management of Refractory Ascites" is not approved anywhere in the world.

SEC Recommendation

First Time Deliberated with 13th SEC Gastroenterology & Hepatology meeting held on 25.07.2018

SEC-recommendation: - "The firm presented their proposal for additional indication of Management of Refractory Ascites along with some clinical data. The committee noted that the drug is not yet approved for the proposed indication in any country.
After detailed deliberation, the committee recommended that the firm should conduct a Phase III clinical trial for the proposed indication. Accordingly, protocol should be submitted for review by the committee".

Second Time Deliberated with 17th SEC Gastroenterology & Hepatology meeting held on 21.02.2019

SEC-recommendation: -"Firm presented the proposal before the committee. The committee observed that the firm couldn't provide justification for present Phase III CT protocol with new indication with supporting scientific data for new proposed indication. Hence, the firm should submit further data for review".

Firm has given the rationality/justification for Clinical Trial Waiver of additional indication as follows:-

- Refractory ascites is defined as ascites that is resistant to high dose diuretic treatment and/or sodium restriction or redevelops rapidly after paracentesis.
- The therapeutic options available for patients with refractory ascites are serial therapeutic paracentesis, liver transplantation, and transjugular intrahepatic portosystemic shunt.Only possible oral drug treatment is via the use of Midodrine before opting the TIPS or liver transplant.
- Midodrine, an α-adrenergic agonist, has been shown to be effectively used in patients with ascites to improve their systemic and renal hemodynamics, clinical outcomes and survival, in support of the claim firm has submitted the published literature.

Recommendation of the committee: After detailed deliberation, the committee recommended that the firm should conduct Phase III clinical trial for which protocol should be for review by the SEC.

The meeting ended with thanks to the Chair

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