SINGH & ASSOCIATES

FOUNDER MANOJ K SINGH

ADVOCATES & SOLICITORS

Vol. II, Issue IX
September 2018

S&A PHARMA NEWSLETTER

EDITORIAL

Manoj K. Singh
Founding Partner

We are pleased to present this Vol. II Issue IX of *S&A – Pharma Newsletter*. Through this Newsletter, we aim to share new or pertinent regulatory information on pharmaceutical sector within India as well as from foreign jurisdictions, based on information collated through research and appraisal of applicable statutory provisions.

In the present issue, we start with a discussion on the Central Government's draft rules on ePharmacy proposed under Drugs and Cosmetics Act, 1945, for stakeholder comments. The draft rules are proposed to regulate the online sale of medicine or ePharmacy business all over the country. Going forward, this edition addresses the release of the first draft 'Charter of patient rights' in the country, which lays down the 17 basic rights of patients with the objective to make these rights functional and enforceable by law. This issue then covers the draft 'Good Distribution Practices guidelines released by CDSCO, to regulate the quality of pharmaceutical products over the entire chain of distribution in the country; followed by a write-up on HIV and AIDS (Prevention and Control) Act, 2017, issued by Health Ministry which seeks to strengthen existing programs by bringing in legal accountability; and establish formal mechanisms for inquiring into complaints and redressing grievances in order to prevent and control the spread of HIV and AIDS.

From the international arena, we talk about recent global survey reports concerning various health issues and the progress on improving health. First, we discuss the 'Global Tuberculosis Report 2018' by WHO, which provides the comprehensive up-to-date assessment of the TB epidemic, and of progress in response to the epidemic, at global, regional and country levels; followed by a note on the first Gene Therapy LUXTURNA® for a genetic vision loss recommended for approval in European Union. The newsletter then has a review on approvals granted in EMA's Committee for Medicinal Products for Human Use meeting in September 2018. We then take a look at the EU approval of Cablivi (caplacizumab), the first therapeutic approved, in Europe, for the treatment of a rare blood-clotting disorder.

We wrap up this newsletter with write-up on United States Food and Drug Administration approval to Lumoxiti (moxetumomab pasudotox-tdfk) injection for intravenous use for the treatment of adult patients with relapsed or refractory Hairy Cell Leukemia (HCL).

Trust you enjoy reading this issue as well. Please feel free to send your valuable inputs / comments at newsletter@singhassociates.in

Thank you.

Contributors to the current issue:
Mr. Manoj K. Singh
Ms. Vijaylaxmi Rathore

All ©Copyrights owned by Singh & Associates

S&A Pharma Newsletter
Volume II, Issue IX
September 2018

SINGH & ASSOCIATES
ADVOCATES & SOLICITORS

NEW DELHI
E-337, East of Kailash
New Delhi - 110065 INDIA

GURUGRAM
7th Floor, ABW Tower, MG Service Road
Sector 25, IFFCO Chowk, Gurugram
Haryana-122001 INDIA

MUMBAI
Unit No. 48 & 49, 4th Floor, Bajaj Bhavan,
Barrister Rajni Patel Marg, Nariman Point,
Mumbai, Maharashtra - 400021, INDIA

BENGALURU
N-304, North Block, Manipal Centre,
47, Dickenson Road
Bengaluru - 560042, INDIA

Ph : +91-11-46667000
Fax : +91-11-46667001

Email: india@singhassociates.in
Website: www.singhassociates.in

www.singhassociates.in

Managing Editor
Manoj K. Singh

Published by
Singh & Associates
Advocates and Solicitors

Contents

Centre proposes draft e-Pharmacy Rules to regulate online sale of drugs

On August 28, 2018, the Central Government proposed ePharmacy draft rules under Drugs and Cosmetics Act 1945 (the Act). The draft rules are proposed to regulate the online sale of medicine or ePharmacy business in India[1]. The draft rules define "e-pharmacy" as a business of distribution or sale, stock, exhibit or offer for sale of drugs through web portal or any other electronic mode. The draft rules also provide for various regulatory processes that would be required to operate ePharmacy business including:

Registration of ePharmacy stores

According to the draft Rule no person shall distribute or sell, stock, exhibit or offer for sale of drugs through e-pharmacy portal unless registered under Central Licensing Authority in Form 18AA through the online portal of the Central Drugs Standard Control Organization (CDSCO). The applicant also needs to pay an application fee of fifty thousand rupees which shall be accompanied with the application form. In additiont to the e-pharmacy registration, the registration holder will have to comply with certain other conditions:

- The e-pharmacy registration holder will have to comply with provisions of Information Technology Act, 2000 (21 of 2000) and Rules made thereunder.
- The e-pharmacy registration holder shall receive the orders for retail sale through e-pharmacy portal.
- The e-pharmacy registration holder shall arrange or provide the drugs, as per the prescription received from the customer, within the period specified by the e-pharmacy registration holder at the time of placement of the order through e-pharmacy portal.
- The supply of any drug shall be made against a cash or credit memo generated through the e-pharmacy portal and such memos shall be maintained by the e-pharmacy registration holder as record.
- The e-pharmacy registration holder shall have a facility for customer support and grievance redressal of all stakeholders which shall run not less than twelve hours for all seven days of a week;

provided, that the facility for customer support shall have registered pharmacist in place to answer the queries of customers through such customer helpline.

The registration issued to any person for e-pharmacy in Form 21AA will remain valid for a period of three years from the date of its issuance and a renewal of registration will have to be done before its expiry in case the entity wants to continue.

Data privacy through e-pharmacy portal

The data of patient received through e-pharmacy portal shall be kept confidential and shall not be disclosed to any other person except to the central government or the concerned state government, in case required for public health purposes. The draft also suggests that in no case the data generated or mirrored through e-pharmacy portal shall be sent or stored, by any means, outside India.

Narcotic and psychotropic drugs sale through e-pharmacy

The e-pharmacy registration holder shall not carry out e-pharmacy activities with respect to the drugs covered under the narcotic and psychotropic categories as referred to in the Narcotic Drugs and Psychotropic Substances

1 http://www.egazette.nic.in/WriteReadData/2018/189043.pdf

Act, 1985 (61 of 1985), tranquilizers and other drugs as specified in the Schedule X of Drugs and Cosmetics Rules, 1945.

Advertisement policy

The draft envisages that no e-pharmacy shall advertise any drug on radio or television or internet or print or any other media for any purpose as per the Drugs and Cosmetics Act, 1940.

Periodic inspection and monitoring

The premises from where the e-pharmacy business is conducted shall be inspected, every two years, by a team of officers authorised by the Central Licensing Authority, with or without the experts in the relevant field or the officers authorised by the concerned State Licensing Authority.

The Central Licensing Authority and the State Licensing Authority shall monitor the data or information of ePharmacy periodically to ensure compliance with the provisions of the Drugs and Cosmetics Act, 1940, and Rules thereunder. Further, the Central Licensing Authority or State Licensing Authority, as the case may be, at any time, may direct any e-pharmacy registration holder to provide prescriptions on the basis of which the drugs have been dispensed for the purpose of transaction audit.

Note- Where the e-pharmacy registration holder contravenes any provision of the Drugs and Cosmetics Act, 1940, and this Rule, the Central Licensing Authority, shall, after giving the e-pharmacy registration holder an opportunity to be heard, shall, by an order and for reasons to be recorded in writing, suspend it for such period as it considers necessary or cancel the registration.

Ministry of Health releases first Patient's Charter in the country

On August 30, 2018, the Ministry of Health and Family welfare notified the first 'Charter of Patient Rights' (the 'Draft Charter') in the country which lays down the 17 basic rights of Patients[2]. Till now the various legal provisions related to patient's rights were scattered across different statutes e.g. the Constitution of India, Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations 2002, the Consumer Protection Act 1986, the Drugs and Cosmetic Act 1940, the Clinical Establishment Act 2010 etc. and other relevant rules / standards framed under each respectively apart from the various judgments given by various legal forums.

This Draft Charter is adopted by the National Human Rights Commission (NHRC), inspired by international charters and guided by national level provisions. The Draft Charter lays down the following 17 basic rights of patients**:**

1. Right to information
2. Right to records and reports
3. Right to emergency medical care
4. Right of informed consent
5. Right to confidentiality, human dignity and privacy
6. Right to second opinion
7. Right to transparency in rates
8. Right to non-discrimination
9. Right to safety and quality care according to standards
10. Right to choose alternative treatment options if available
11. Right to choose source for obtaining medicine and tests
12. Right to proper referral and transfer, which is free from perverse commercial influence
13. Right to protection for patients involved in clinical trials
14. Right to protection of participants involved in biomedical and health research
15. Right to take discharge of patient, or receive body of deceased from hospital
16. Right to Patient Education
17. Right to be heard and seek redressal

This Draft Charter draws upon all relevant provisions, inspired by international charters and is guided by national level provisions, with the objective of consolidating these into a single document, thereby making them publicly known in a coherent manner. There is an expectation that this document will act as a guidance document for the Union and State Governments to formulate concrete mechanisms so that patient's rights are given adequate protection and operational mechanisms can be set up to make these rights functional and enforceable by law.

Another objective of this Draft Charter is to generate widespread public awareness and educate citizens regarding what they should expect from their governments and health care providers about the kind of treatment they deserve as patients and human beings, in health care settings.

Responsibilities of patients and caretakers

The Draft Charter, along with promoting patient's rights, also explains the responsibilities of patients and caretakers so that hospitals and doctors can perform their work satisfactorily -

1) Patients should provide all required health related information to their doctor, so that diagnosis and treatment can be facilitated.

2 https://www.mohfw.gov.in/sites/default/files/PatientCharterforcomments.pdf

2) Patients should cooperate with the doctor during examination, diagnostic tests and treatment, and should follow doctor's advice, while keeping in view their right to participate in decision making related to treatment.
3) Patients should follow all instructions regarding appointment time, cooperate with hospital staff and fellow patients, avoid creating disturbance to other patients, and maintain cleanliness in the hospital.
4) Patients should respect the dignity of the doctor and other hospital staff as human beings and as professionals. Whatever the grievance may be, patient / caregivers should not resort to violence in any form and damage or destroy any property of the hospital or the service provider.
5) Patients should take responsibility for their actions based on choices made regarding treatment options, and in case they refuse treatment.

Grievance redressal mechanism

According to NHRC, the Government of India, all State Governments and administration of Union Territories, as a component of their existing or emerging regulatory frameworks for clinical establishments, should have a Patients' rights grievance redressal mechanism for patients. Further, the grievance redressal mechanism should have these three levels of hierarchy: 1) Internal grievance redressal mechanism; 2) District level registering authority; and 3) State Council of Clinical Establishments under Clinical Establishment (Registration and Regulation) Act 2010 for managing relevant complaints.

Apart from the above-mentioned grievance redressal mechanisms, patients/representatives would always be free to approach the State Medical Council to seek disciplinary action against unethical conduct of any specific doctor, and to seek redressal from consumer forums at various levels for financial compensation, or approach Civil/Criminal Courts keeping in view the nature of the complaint.

Note – The Draft Charter is available at Health Ministry website and open for stakeholder comments. Once finalized, it will be circulated and prominently displayed at all hospitals, clinics, pharmacies etc. The charter is meant to generate widespread public awareness and educate citizens regarding what they should expect from their governments and health care providers, about the kind of treatment they deserve as patients and human beings.

CDSCO proposes Good Distribution Practices draft guideline for pharmaceutical products

On September 25, 2018, the Central Drugs Standard Control Organization (CDSCO) has released the draft guidelines on 'Good Distribution Practices' (GDP) to regulate the quality of pharmaceutical products over entire chain of distribution in the country[3].

The idea of GDP was initially deliberated in the 54th Drug Consultative Meeting held on July 07, 2018, and it was recommended to take necessary provisions to impart legal sanctity to the 'GDP Guidelines' as a Schedule to the Drug & Cosmetics Rules, 1945 (the 'Rules') to penalize the offenders[4].

According to a recent World Health Organization (WHO) report[5], an estimated 01 in 10 medical products circulating in low- and middle-income countries like India, is either substandard or falsified. According to the UN agency, these medicines not only fail to treat or prevent diseases but can also cause serious illnesses or even death. Further, the first-ever national drug survey 2014-16[6], conducted by the union Ministry of Health and Family Welfare, shows that over 3% of all drugs sold across India are of substandard quality.

The objective of these draft guidelines is to ensure the quality and identity of pharmaceutical products during all aspects of the distribution process. These aspects include, but are not limited to procurement, purchase, storage, distribution, transportation, documentation and record-keeping practices. These guidelines are intended to be applicable to all persons and outlets involved in trade and distribution of pharmaceuticals, including the manufacturers of bulk, finished products, wholesalers, as well as others such as suppliers, distributors, Government institutions, international procurement organizations, donor agencies and certifying bodies, logistics providers, traders, transport companies and forwarding agents and their employees as well as health workers. It also covers biological products in general.

Documentation and records

The guidelines lay out various measures to guarantee that medicines entering the distribution chain have proper documentation to permit traceability. Records of expiry dates and batch numbers should be part of the documentation to facilitate product recall. Moreover, procedures for procurement and release shall be in place to ensure that appropriate products are sourced only from approved suppliers and distributed by recognised entities. Inspection, auditing and certification of compliance with a quality system such as the ISO series or national guidelines by external bodies are recommended.

Storage and transportation

The guideline suggests that the storage and transportation of pharmaceutical products should match the storage conditions indicated on the packaging/labelling information. The individuals responsible for the transportation of pharmaceutical products shall be informed about all relevant conditions for storage and transportation and these requirements shall be adhered to throughout the transportation and at any intermediate storage stages.

The entire storage facility should be temperature mapped under representative conditions. Equipment used for monitoring of storage conditions shall also be calibrated at defined intervals. Where special conditions are

3 http://cdsco.nic.in/writereaddata/Notice-25_09_2018_Draft%20Guidelines%20on%20Good%20Distribution%20Practices%20for%20Pharmaceutical%20Products.pdf

4 http://cdsco.nic.in/writereaddata/Report%20of%2054th%20DCC%20Meeting%20held%20on%2030_07_2018.pdf

5 http://www.who.int/news-room/detail/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandard-or-falsified

6 http://www.indiaenvironmentportal.org.in/files/file/National%20Drug%20Survey%202014-16.pdf

required during transportation that are different from or limit the given environmental conditions (e.g. temperature and humidity), these shall be provided by the manufacturer on the labels and shall be monitored and recorded. If a deviation has occurred during transportation, it shall be reported to the distributor and recipient of the affected pharmaceutical products.

Recalls and Returns

The guideline envisages there shall be a system of written procedure for the management of recalls of defective pharmaceutical products with a designated person responsible for recalls. The system of recall shall comply with Drugs & Cosmetics Act, 1940 and Rules thereunder.

Recall operations shall be capable of being initiated promptly and at any time. The distributor shall follow the instructions of a recall message, the distribution records shall be readily available to the person(s) responsible for the recall and shall contain sufficient information on distributors and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and quantities delivered). Recalled pharmaceutical products shall be identified and stored separately in a secure area while awaiting a decision on their disposal.

Note – The Draft GDP Guidelines for Pharmaceutical Products is available on CDSCO official website and is open for stakeholder comments/feedback, further for consideration and finalization of said Guidelines.

Health Ministry releases HIV and AIDS (Prevention and Control) Act, 2017

On September 10, 2018, the Ministry of Health and Family Welfare notified "*Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (Prevention and Control) Act, 2017*" (Hereinafter called 'Act') with immediate effect[7]. The Act had already received Presidential assent in April 2017 and was notified after Hon'ble Delhi High Court's intervention seeking immediate notification to protect and secure the human rights of persons affected with HIV/Acquired Immune Deficiency Syndrome (AIDS).

India has the world's third largest population of people with HIV/AIDS after South Africa and Nigeria[8]. According to the prevalence estimates released by the National AIDS Control Organisation (NACO), India had around 2.14 million people living with HIV in 2017, which includes 0.22% of people in the 15-49 years age group in the country. India saw around 87,580 new HIV infections and 69,110 AIDS related deaths in 2017.

The Act seeks to prevent and control the spread of HIV and AIDS; strengthen existing program by bringing in legal accountability; and establish formal mechanisms for inquiring into complaints and redressing grievances.

Prohibition of discrimination

The Act prohibits discrimination against persons with HIV and AIDS. It lists various grounds on which discrimination against HIV positive persons and those living with them, is prohibited. These discrimination grounds include denial, termination, discontinuation or unfair treatment with regard to employment, educational establishments, health care services, standing for public or private office, residing or renting property and provision of insurance. It also prohibits the isolation of protected persons and requirement for HIV testing as pre-requisite for obtaining employment or accessing health care or education.

The Act prohibits hatred and physical violence

No person shall, by words, either spoken or written, publish, propagate, advocate or communicate by signs or by visible representation or otherwise, the feelings of hatred against HIV positive person or affected groups, or which may reasonably be construed to demonstrate an intention to propagate hatred or discrimination or physical violence.

Disclosure of HIV status

No person shall disclose or be compelled to disclose the HIV status or HIV-related information except with the informed consent for undertaking HIV tests, medical treatment and research; or by an order of the court that the disclosure of such information is necessary in the interest of justice.

The Act also describes the eligibility of a person between the age of 12 to 18 years, who has enough maturity for understanding and managing the affairs of his HIV or AIDS affected family, shall be competent to act as a guardian of another sibling below 18 years of age.

Informed consent not mandatory for conducting HIV tests in certain cases

Informed consent is not mandatory if : i) it is by an order of court that HIV testing of any person, as part of a medical examination or otherwise, is necessary for the determination of issues in the matter before it; ii) it is for testing of a donor donating human body/any parts prior to donation; iii) it is for epidemiological or surveillance

7 http://www.egazette.nic.in/WriteReadData/2018/189234.pdf

8 http://naco.gov.in/sites/default/files/HIV%20Estimations%202017%20Report.zip

purposes where the HIV test is anonymous and is not for the purpose of determining the HIV status of a person; or iv) if it is for screening purposes in any licensed blood bank.

However, no HIV test shall be conducted or performed by any testing or diagnostic centre or pathology laboratory or blood bank, unless such centre or laboratory or blood bank complies with the guidelines laid down for such test.

The role of Central Government and State Government

The Central Government or the State Government shall issue necessary guidelines including the measures for providing, as far as possible, diagnostic facilities relating to HIV or AIDS, Anti-retroviral Therapy and Opportunistic Infection Management to people living with HIV or AIDS, and also:

- shall take measures to facilitate better access to welfare schemes to persons infected or affected by HIV or AIDS;
- shall frame schemes to address the needs of all protected persons;
- shall take appropriate steps to protect the property of children affected by HIV or AIDS;
- shall formulate HIV and AIDS related information, education and communication programmes which are age-appropriate, gender-sensitive, non-stigmatising and non-discriminatory;
- shall lay down guidelines for care, support and treatment of children infected with HIV or AIDS; and
- shall take measures to counsel and provide information regarding the outcome of pregnancy and HIV-related treatment to the HIV infected women. No HIV positive woman, who is pregnant, shall be subjected to sterilization or abortion without obtaining her informed consent[9].

The state government shall appoint one or more ombudsman to inquire into complaints related to the violation of the provisions of this Act and the provisions of health care services.

Note: If any difficulty arises in giving effect to the provisions of this Act, the Central Government may, by order published in the Official Gazette, make such provisions, not inconsistent with the provisions of this Act, as may appear to be necessary for removing the difficulty, within two year from commencement of this Act.

9 http://naco.gov.in/sites/default/files/HIV%20AIDS%20Act.pdf

India accounted for almost quarter of the world's cases of MDR/ RR-TB: WHO report

WHO calls for urgent action to end Tuberculosis (TB) as it estimates that a quarter of the world's population has TB infection

On September 18, 2018, World Health Organization (WHO) published a 'Global TB Report 2018[10]' in the lead up to the UN high-level meeting on TB. This 2018 edition of global report on TB provides a comprehensive and up-to-date assessment of the TB epidemic, and of progress in the response to the epidemic, at global, regional and country levels[11].

TB is one of the top 10 causes of death and the leading fatal cause from a single infectious agent. Millions of people continue to fall sick with TB each year. Although global efforts have averted an estimated 54 million TB deaths since 2000, TB remains the world's deadliest infectious disease. This report calls for an unprecedented mobilization of national and international commitments. It urged political leaders who gathered for the first-ever United Nations High-level Meeting on September 26, 2018, to take decisive action towards ending the TB epidemic[12].

The highlights of Global TB Report 2018 briefing India status

Reporting new TB cases: Worldwide in 2017, 6.4 million new cases of TB were officially notified to national authorities and then reported to WHO. From 5.7-5.8 million cases reported in 2013, this number has increased to 6.4 million mainly due to increased reporting of cases detected by the private sector in India and Indonesia.

The severity of national epidemics varies widely among countries. In 2017, there were fewer than 10 new cases per 100 000 population in most high-income countries, 150–400 in most of the 30 high TB burden countries, and above 500 in a few countries including Mozambique, the Philippines and South Africa.

Notification of TB: Globally in 2017, 60% of notified TB patients had a documented HIV test result, up from 58% in 2016. Despite increases in notifications of TB, progress in closing detection and treatment gaps is slow and large gaps remain. India accounts 26% of this global gap, and the total gap with Indonesia (11%), Nigeria (9%) and the Philippines (7%) accounts for more than half of the global total.

Drug resistant TB: Drug-resistant TB continues to be a public health crisis. Worldwide in 2017, 558 000 people developed TB that was resistant to rifampicin (RR-TB), the most effective first line drug, and of these, 82% had multidrug-resistant TB (MDR-TB). Three countries together accounted for almost half of the world's cases of MDR/ RR-TB - India (24%), China (13%) and the Russian Federation (10%).

Globally, the 139 114 patients starting second-line MDR-TB treatment in 2017, represented 25% of the 558 000 estimated MDR/RR-TB incident cases for the same year. China and India together accounted for 40% of the total gap between enrolments in MDR-TB treatment in 2017 and the estimated number of incident MDR/RR-TB cases in 2017.

10 http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf

11 http://www.who.int/tb/publications/global_report/Exec_summary_17Sept2018.pdf

12 http://www.who.int/news-room/detail/18-09-2018-who-calls-for-urgent-action-to-end-tb-

Treatment Success Rate: Among the six WHO regions, the highest treatment success rate in 2016 was in the WHO Eastern Mediterranean Region (92%). The lowest treatment success rate (at 75%) was in the WHO South-East Asia Region (due to high proportions of unevaluated cases, especially in India).

A total of 292 182 children aged under 5 years were reported to have been initiated on TB preventive treatment in 2017, an increase of 79% from 163 720 in 2016. At country level, India reported the largest number (38 745), followed by South Africa (32 104).

TB mortality in 2017: TB is the tenth leading cause of death worldwide, and since 2011 it has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS. Globally, there were an estimated 1.3 million deaths from TB among HIV-negative people in 2017 and an additional 300 000 (range, 266 000–335 000) deaths from TB among HIV-positive people. India accounted for 32% of global TB deaths among HIV-negative people, and for 27% of the combined total TB deaths in HIV-negative and HIV-positive people.

Financing for TB prevention, diagnosis and treatment: Funding for the provision of TB prevention, diagnosis and treatment services has more than doubled since 2006. As in previous years, most of the funding (86%) available in 2018 is from domestic sources. However, this global aggregate figure is strongly influenced by BRICS, in which 96% of funding is from domestic sources. In India, domestic funding more than tripled between 2016 and 2018.

TB case-finding among people attending HIV care in India: For the past year, the Revised National TB Control Programme (RNTCP) and National AIDS Control Organization (NACO) in India have been capturing data to evaluate TB case-finding activities among people attending ART centres.

According to data reported by the RNTCP for 2017, an estimated 58% (n = 49 000) of people with HIV-associated TB were not reported to have reached TB care. Reasons for missing people with TB include poor access to services, weaknesses in service delivery, and gaps in recording and reporting, and limited engagement of the private sector.

Note – For the matter of this report, the estimates of TB incidence and mortality for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.

First Gene Therapy LUXTURNA® for a genetic vision loss recommended for approval in European Union

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for the gene therapy Luxturna (voretigene neparvovec), for the treatment of adults and children suffering from Inherited Retinal Dystrophy (IRD) caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness[13,14].

Luxturna is meant for patients with confirmed biallelic mutations of the RPE65 gene (i.e. patients who have inherited the mutation from both parents) but who have sufficient viable retinal cells. It is the first gene therapy to be recommended for approval for a retinal disease.

The approval was supported by Phase 1 clinical trial, its follow-up trial and a Phase 3 trial that together enrolled 43 participants with inherited retinal disease caused by mutations on both copies of the RPE65 gene. The Phase 3 trial was the first randomized, controlled Phase 3 gene therapy trial for a genetic disease. The applicant for Luxturna is Spark Therapeutics Ireland Ltd.

The CHMP's opinion is based on the assessment by EMA's expert committee on Advanced Therapy Medicinal Products (ATMPs), the Committee for Advanced Therapies (CAT). Luxturna was designated as an orphan medicine and an ATMP, and EMA provided protocol assistance to the applicant during the development of the medicine.

About IRD by RPE65 gene mutations

Inherited retinal diseases (also known as inherited retinal dystrophies) are a group of rare blinding conditions caused by one of more than 220 different genes, often disproportionally affecting children and young adults. The mutations of the RPE65 gene, which encodes one of the enzymes involved in the biochemistry of light capture by the cells of the retina, hinder the patient's ability to detect light. It is a severely debilitating disease, characterised by a progressive loss of vision. Most patients will be blind by the time they are young adults. There is currently no treatment for this disease; support to patients is limited to measures allowing the management of the disease such as aids for low vision.

About Luxturna

Luxturna works by delivering a functional RPE65 gene into the cells of the retina through a single retinal injection, which restores the production pathway for the required enzyme thereby improving the patient's ability to detect light. Patients must have viable retinal cells as determined by the treating physicians.

Note - A marketing authorization decision from the European Commission is anticipated approximately within two months. If approved, the authorization will be valid in all 28-member states of the European Union, as well as Iceland, Liechtenstein and Norway. In January 2018, Spark Therapeutics entered into a licensing and supply agreement with Novartis to commercialize LUXTURNA when and if approved in Europe and in all markets outside the U.S. LUXTURNA would be first gene therapy for a genetic disease approved in both U.S. and EU.

13 https://www.ema.europa.eu/news/new-gene-therapy-rare-inherited-disorder-causing-vision-loss-recommended-approval

14 http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-announces-positive-chmp-opinion-one-time-gene

European Medicines Agency (EMA): Recommends approval of thirteen medicines in its September meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended thirteen medicines for approval, including three orphan medicines, at its September 2018 meeting[15]. The approvals include the first gene therapy Luxturna for the treatment of adults and children with a rare inherited retinal dystrophy disease, and Emgality, a new class of drug for prevention of migraine.

A) The thirteen medicines recommended for approval are:

Sl. No.	Name of Medicine	Indicated For	Marketing-Authorisation Holder
1	Luxturna (voretigene neparvovec)	Treatment of retinal dystrophies caused by RPE65 mutations	Spark Therapeutics Ireland Ltd
2	Emgality (galcanezumab)	Prophylaxis of migraine	Eli Lilly Nederland B.V.
3	Vabomere (meropenem / vaborbactam)	Treatment of the following infections in adults: - Complicated urinary tract infection (cUTI), including pyelonephritis - Complicated intra-abdominal infection (cIAI) - Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).	Rempex London Ltd
4	Jivi (damoctocog alfa pegol)	Treatment of haemophilia A (congenital factor VIII deficiency	Bayer AG
5	Poteligeo (mogamulizumab)	Treatment of mycosis fungoides or Sézary syndrome	Kyowa Kirin Limited
6	Alunbrig (brigatinib)	Treatment of adult patients with anaplastic lymphoma kinase positive advanced non-small cell lung cancer previously treated with crizotinib	Takeda Pharma A/S
7	Apealea (paclitaxel)	Treatment of ovarian cancer	Oasmia Pharmaceutical AB
8	Delstrigo (doravirine / lamivudine / tenofovir disoproxil)	Treatment of HIV-1 infection	Merck Sharp & Dohme B.V.
9	Pifeltro (doravirine)	Treatment of HIV-1 infection	Merck Sharp & Dohme B.V.
10	Fulphila (pegfilgrastim)	To reduce the duration of neutropenia and the incidence of febrile neutropenia due to chemotherapy	MYLAN S.A.S
11	Pelmeg (pegfilgrastim)	To reduce the duration of neutropenia and the incidence of febrile neutropenia due to chemotherapy	Cinfa Biotech S.L.
12	Ziextenzo (pegfilgrastim)	To reduce the duration of neutropenia and the incidence of febrile neutropenia due to chemotherapy	Sandoz GmbH
13	Buvidal (buprenorphine)	Treatment of opioid dependence	Camurus AB

15 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/09/news_detail_003019.jsp&mid=WC0b01ac058004d5c1

B) Negative recommendations on new medicines following re-examination

The CHMP has issued a negative recommendation for one drug Exondys (eteplirsen), intended for the treatment of Duchenne muscular dystrophy. The applicant company, AVI Biopharma International Ltd, had requested a re-examination of the CHMP's opinion on June 01, 2018. After considering the grounds for this request, the CHMP re-examined the opinion, and confirmed the refusal of the marketing authorization[16].

C) CHMP recommendations on extensions of therapeutic indication

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended a change to the terms of the marketing authorisation for seven drugs on extensions of therapeutic indication as described in table (*New indications are marked in bold, and deleted indications are marked in strikethrough*)

Sl. No.	Name of medicine	Full Indication	Marketing-authorisation holder
1	Cabometyx (cabozantinib)	CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC): - in treatment-naïve adults with intermediate or poor risk (see section 5.1) - in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy **Hepatocellular Carcinoma (HCC)** **CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib**.	Ipsen Pharma
2	Elebrato Ellipta (fluticasone furoate / umeclidinium / vilanterol fluticasone)	Elebrato Ellipta is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom control and prevention of exacerbations)	GlaxoSmithKline Trading Services Limited
3	Gilenya (fingolimod)	Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and **paediatric patients aged 10 years and older**: -Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or -Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	Novartis Europharm Limited

16 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004355/WC500249920.pdf

Sl. No.	Name of medicine	Full Indication	Marketing-authorisation holder
4	RoActemra (tocilizumab)	RoActemra, in combination with methotrexate (MTX), is indicated for: - the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX. - the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. **RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.** RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.	Roche Registration GmbH
5	Trelegy Ellipta (fluticasone furoate / umeclidinium / vilanterol fluticasone)	Trelegy Ellipta is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or **a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist.**	GlaxoSmithKline Trading Services Limited

Sl. No.	Name of medicine	Full Indication	Marketing-authorisation holder
6	Venclyxto (venetoclax)	**Venclyxto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.** Venclyxto monotherapy is indicated for the treatment of ~~chronic lymphocytic leukaemia (CLL)~~: -in the presence of 17p deletion or **TP53** mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, **or** ~~-Venclyxto monotherapy is indicated for the treatment of CLL~~ in the absence of 17p deletion or **TP5**3 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor.	AbbVie Deutschland GmbH & Co. KG
7	Xtandi (enzalutamide)	Xtandi is indicated for: **-the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).** -the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. -the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.	Astellas Pharma Europe B.V.

D) Update on valsartan review

The European Medicines Agency (EMA) is expanding its review of impurities in valsartan following the detection of very low levels of N-nitrosodiethylamine (NDEA) in another active substance, losartan, made by Hetero Labs in India. As a result of the detection of this impurity by German authorities, the review will now include medicines containing four other 'sartans', namely, candesartan, irbesartan, losartan and olmesartan. These active substances have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of impurities such as NDEA. Other medicines of the class which do not have this ring are not included in the review[17].

E) Withdrawals of applications

Applications for initial marketing authorisations for Entolimod TMC (entolimod) and Treprostinil SciPharm Sàrl (treprostinil) have been withdrawn. Treprostinil SciPharm Sàrl was intended to be used to treat chronic thromboembolic pulmonary hypertension.

Note - The CHMP's assessments are based on a comprehensive scientific evaluation of data. They determine whether the medicine meets the necessary quality, safety and efficacy requirements and that it has a positive risk-benefit balance. The CHMP carry out a scientific assessment of the application and give a recommendation on whether the medicine should be marketed or not. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway.

17 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/09/news_detail_003023.jsp&mid=WC0b01ac058004d5c1

Cablivi is the first therapeutic approved, in Europe, for the treatment of a rare blood-clotting disorder

On September 03, 2018, the European Commission has granted marketing authorization for Cablivi™ (caplacizumab) for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood-clotting disorder. Cablivi is the first therapeutic specifically indicated for the treatment of aTTP[18]. Cablivi was designated an 'orphan medicine' (a medicine used in rare diseases) on April 30, 2009.

The approval of Cablivi in the EU is based on the Phase II TITAN and Phase III HERCULES studies in 220 adult patients with aTTP. The efficacy and safety of caplacizumab in addition to standard-of-care treatment, daily PEX and immunosuppression, were demonstrated in these studies. In the HERCULES study, treatment with caplacizumab in addition to standard-of-care resulted in a significantly shorter time to platelet count response ($p<0.01$), the study's primary endpoint; a significant reduction in aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event during study drug treatment ($p<0.0001$); and a significantly lower number of aTTP recurrences in the overall study period ($p<0.001$). Importantly, treatment with caplacizumab resulted in a clinically meaningful reduction in the use of PEX and length of stay in the intensive care unit (ICU) and the hospital, compared to the placebo group.

Cablivi was developed by Ablynx, a Sanofi company. Sanofi Genzyme, the specialty care global business unit of Sanofi, will work with relevant local authorities to make Cablivi available to patients in need in countries across Europe.

About aTTP

aTTP is a life-threatening, autoimmune blood clotting disorder characterized by extensive clot formation in small blood vessels throughout the body, leading to severe thrombocytopenia (very low platelet count), microangiopathic hemolytic anemia (loss of red blood cells through destruction), ischemia (restricted blood supply to parts of the body) and widespread organ damage especially in the brain and heart.

About Cablivi

Caplacizumab blocks the interaction of ultra-large von Willebrand Factor (vWF) multimers with platelets and, therefore, has an immediate effect on platelet adhesion and the ensuing formation and accumulation of the micro-clots that cause the severe thrombocytopenia, tissue ischemia and organ dysfunction in aTTP[19].

Note - Caplacizumab is a bivalent anti-vWF Nanobody that received Orphan Drug Designation in Europe and the United States in 2009, in Switzerland in 2017 and in Japan in 2018. The U.S. Food and Drug Administration (FDA) has accepted for priority review the Biologics License Application for caplacizumab for treatment of adults experiencing an episode of aTTP. The target action date for the FDA decision is February 6, 2019.

18 http://hugin.info/152918/R/2213684/863478.pdf

19 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004426/WC500255075.pdf

USFDA approval to Lumoxiti is a new treatment for hairy cell leukemia

On September 13, 2018, the U.S. Food and Drug Administration approved Lumoxiti (moxetumomab pasudotox-tdfk) injection for intravenous use for the treatment of adult patients with relapsed or refractory Hairy Cell Leukemia (HCL) who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog[20]. Lumoxiti is a CD22-directed cytotoxin and is the first of this type of treatment for patients with HCL.

The efficacy of Lumoxiti was studied in a single-arm, open-label clinical trial of 80 patients who had received prior treatment for HCL with at least two systemic therapies, including a purine nucleoside analog. The trial measured durable complete response (CR), defined as maintenance of hematologic remission for more than 180 days after achievement of CR. Thirty percent of patients in the trial achieved durable CR, and the overall response rate (number of patients with partial or complete response to therapy) was 75 percent.

The FDA granted this application Fast Track and Priority Review designations. Lumoxiti also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases. The FDA granted the approval of Lumoxiti to AstraZeneca Pharmaceuticals.

About Hairy Cell Leukemia

HCL is a rare, slow-growing cancer of the blood in which the bone marrow makes too many B cells (lymphocytes), a type of white blood cells that fight infection. HCL is named after these extra B cells which look "hairy" when viewed under a microscope. As the number of leukemia cells increases, fewer healthy white blood cells, red blood cells and platelets are produced.

About Lumoxiti[21]

Lumoxiti (moxetumomab pasudotox) is a CD22-directed cytotoxin and a first-in-class treatment in the US for adult patients with relapsed or refractory hairy cell leukaemia (HCL) who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog. Lumoxiti is not recommended in patients with severe renal impairment (CrCl ≤ 29 mL/min). It comprises the CD22 binding portion of an antibody fused to a truncated bacterial toxin; the toxin inhibits protein synthesis and ultimately triggers apoptotic cell death.

***

20 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620448.htm

21 https://www.astrazeneca.com/media-centre/press-releases/2018/us-fda-approves-lumoxiti-moxetumomab-pasudotox-tdfk-for-certain-patients-with-relapsed-or-refractory-hairy-cell-leukaemia.html

SINGH & ASSOCIATES

FOUNDER MANOJ K SINGH

ADVOCATES & SOLICITORS

NEW DELHI
E-337, East of Kailash
New Delhi - 110065, INDIA

GURUGRAM
7th Floor, ABW Tower, MG Service Road
Sector 25, IFFCO Chowk, Gurugram
Haryana - 122001, INDIA

MUMBAI
Unit No. 48 & 49, 4th Floor
Bajaj Bhavan, Nariman Point
Mumbai - 400021, INDIA

BENGALURU
N-304, North Block, Manipal Centre
47, Dickenson Road
Bengaluru - 560042, INDIA

india@singhassociates.in
www.singhassociates.in