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S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

We are pleased to present this Vol. II Issue XII 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 measures taken by the Central Drugs Standard Control Organization (CDSCO) by changing/amending the Drugs and Cosmetic Rule, 1945, to ensure the quality of drugs manufactured/ marketed in the country. Going forward, this edition addresses the Delhi High Court's order banning online sale of medicines which will continue till the new policy and/or framework regulating e-pharmacy is enforced by government. The issue then, covers the CDSCO's safety guidance on 'Isotretinoin', which cautioned that the drug may cause severe birth defects in pregnant, or may likely to become pregnant patients during the course of treatment. The next article then, covers the Central Government announcement banning the use of Buclizine as '*appetite stimulant*' which was found to be irrational for the said indication. However, the same will be available in the market for the "*symptomatic treatment of various allergic conditions (rhinitis, conjunctivitis and urticaria) and for prevention and treatment of motion sickness*".

From the international arena, we talk about recent regulatory reforms concerning various health issues and the health reports focusing on improving health in countries. First, we discuss the launch of pilot project, which is jointly initiated by U.S. Food and Drug Administration (USFDA) and World Health Organization (WHO), to speed up approval of HIV medicines for supply to developing countries. This article is followed by a write-up on European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) meeting December 2018, which recommended approval of seven medicines including two orphan medicines. The said committee also recommended the extensions of therapeutic indications of six medicines in this meeting.

We wrap up this issue with US FDA approvals - 1) Sanofi's new pediatric vaccine 'VAXELIS™' indicated for active immunization to prevent six diseases - diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to Haemophilus influenzae type b and 2) Elzonris (tagraxofusp-erzs) infusion and Ultomiris (ravulizumab) injection indicated for the treatment of rare blood diseases, BPDCN and PNH respectively.

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

Thank you.

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Measures taken by CDSCO under D&C Rule to ensure quality of drugs in the year 2018

Central Drugs Standard Control Organization (CDSCO), in coordination with concerned State Licensing Authority for action as per the provisions of Drugs & Cosmetics Act, 1940 (the 'Act'), and the Drugs & Cosmetics Rules, 1945 (the 'Rules'), has taken various measures by way of bringing about certain amendments in the existing regulations, to ensure the quality of drugs including generic drugs manufactured / marketed in the country. In the year 2018, there were a total of ten amendments in the Rules. The brief details of amendments are as under:

1. Printing Drug's Generic Names in Bigger, Bolder Font than Brand Name

On March 13, 2018, the Drugs and Cosmetics (First Amendment) Rules, 2018 notified under Gazette notification no. G.S.R. 222 (E) amended Rule 96 of the Rules. The amended rule now provides that the proper name of the drugs (generic) shall be printed in a conspicuous manner which shall be in the same font but at least two font size larger than the brand name or the trade name, if any[1]. According to the Drugs and Cosmetics (Eighth Amendment) Rules, 2018, the labelling requirement shall be on a voluntary basis for a period from 13.09.2018 to 31.03.2019 and thereafter shall be mandatory[2].

2. Steroidal drugs are included under Schedule H of Drugs and Cosmetics Act, 1940

Vide Gazette notification no. G.S.R. 277(E) dated March 23, 2018 the Drugs and Cosmetics (Second Amendment) Rules, 2018 were notified thereby updating Schedule H provided under the Rules, with addition of 14 Steroidal drugs - Alclometasone, Beclomethasone, Betamethasone, Desonide, Desoximetasone, Dexamethasone, Diflorasone diacetate, Fluocinonide, Fluocinolone acetonide, Halobetasol propionate, Halometasone, Methylprednisone, Prednicarbate, and Triamcinolone acetonide - making them prescription drugs for patient use[3].

3. CDSCO mandates the submission of stability data of all drugs before granting product license

On April 10, 2018, the Drugs and Cosmetics (Third Amendment) Rules were notified vide Gazette notification no. G.S.R. 360 (E), 2018, for replacing the words 'patent or proprietary medicines' with the word ' drugs' of rules 71, 71b, 76, 76A, and schedule D of the Rules; which now makes it mandatory to submit stability data etc. for all drugs by applicant as per the provision before grant of product license by the respective State Licensing Authority[4].

4. Inclusion of Oxygen 93% supplied from liquid oxygen for production of Oxygen 93% USP under Schedule K

Vide Gazette notification no. G.S.R. 385(E) dated April 19, 2018, the Drugs and Cosmetics (Fourth Amendment) Rules, 2018, amended the Rules, and thereby included under Schedule K, Oxygen 93% supplied from liquid oxygen in the production of Oxygen 93% USP by a hospital or medical institute for their captive consumption, in addition to oxygen being produced from air by the molecular sieve process. Making it under Schedule K provides exemption from the applicability of provisions of Chapter IV (Manufacture, Sale and Distribution of Drugs and

1 http://egazette.nic.in/WriteReadData/2018/183769.pdf

2 https://lexcomply.com/rsjadmin/news/201812195052Notification%20GSR%201161(E)-%20%20Drugs%20and%20Cosmetics%208th%20Amendment%20Rules%202018.pdf

3 http://www.cdsco.nic.in/writereaddata/GSR%20277(E)%20dated%2023_03_2018.pdf

4 http://www.cdsco.nic.in/writereaddata/GSR%20360(E)%20dated%2010_04_2018.pdf

Cosmetics) of the Act, and the rules provided that the production facilities shall be open to inspections by an Inspector appointed under the said Act[5].

5. Central Government notify labeling specification of Schedules G, H, H1 and Schedule X drugs

On April 26, 2018, the Drugs and Cosmetics (Fifth Amendment) Rules, 2018 notified vide Gazette notification no. G.S.R. 408(E), updated the labeling specification of inner most container of the following categories of drugs and every other covering in which the container is packed shall bear a caution or warning, as applicable, depending on whether the drug is covered under Schedule G or Schedule H or Schedule H1 or Schedule X, as specified in Rule 97, in legible black coloured font size in a completely red rectangular box without disturbing other conditions printed on the label under these rules.

The labelling specification applies on narcotic analgesics, hypnotics, sedatives, tranquillisers, corticosteroids, hormones, hypoglycemic, antimicrobials, antiepileptics, antidepressants, anticoagulants, anti-cancer drugs and all other drugs falling under Schedules G, H, H1 and Schedule X whether covered or not in the said schedules[6].

6. Extended validity of Drug import license for personal use

On June 01, 2018, the Drugs and Cosmetics (Sixth Amendment) Rules, 2018 notified vide Gazette notification no. G.S.R. 521(E) updated Form 12B, which now allows permit holder to import the medication for personal use till such time as the patient requires the drug as per the prescription of a registered medical practitioner, and the permit holder shall submit details of drugs imported and utilized to the licensing authority on yearly basis, which was for only six month period earlier[7].

7. Oxytocin reclassified as Schedule H1

Vide Gazette notification no. G.S.R. 795(E) dated August 21, 2018, the Drugs and Cosmetics (Seventh Amendment) Rules, 2018 reclassified oxytocin from the list of Schedule H drugs to Schedule H1 drug under the Rules, which requires retail chemists to document the customer and physician details for each sale for at least 3 years further to check the indiscriminate use of drug[8].
Moreover, the Central Government also announced the strict regulatory control over manufacture, sale and distribution of oxytocin this year to curb its misuse under section 26A of the Act.

8. Clarification in case of use of colors in empty gelatin capsules (Hard and Soft)

On December 07, 2018, the Drugs and Cosmetics (Ninth Amendment) Rules, 2018 notified vide Gazette notification no. G.S.R. 1186(E) amended Rule 127, that in the manufacture of gelatine capsule approved/permitted colours shall be used and drug label containing gelatine capsules need not indicate the name of colour added as more than one colours are quite often used[9].

9. Revised regulatory fees for various drug licensing activities

On December 12, 2018, the Drugs and Cosmetics (Tenth Amendment) Rules, 2018 notified vide Gazette notification no. G.S.R. 1193(E) revised regulatory fee and increased the fee for site registration, product approval,

5 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=OTM0

6 http://www.cdsco.nic.in/writereaddata/gsr408.pdf

7 http://www.egazette.nic.in/WriteReadData/2018/186082.pdf

8 http://egazette.nic.in/WriteReadData/2018/188704.pdf

9 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MjM1OA

licenses for import of drugs and medical devices, permissions for clinical trials and import of drugs for tests and overseas inspections[10]. Notable, the Central government last updated this fee in 2003.

10. Mandatory unique ID number system to keep a check on misleading advertisement for ASU drugs

On December 21, 2018 the drug and cosmetics (Eleventh amendment) Rules 2018 notified vide gazette notification no. G.S.R. 1230(E) inserted new Rule 170 in Rules, introduced unique ID number system for Ayurvedic, Siddha and Unani (ASU) medications sold in the country, which provide a stringent regulatory check for misleading and inappropriate advertisements. As per the new notification, if the drug is not intended for therapeutic purpose, for instance a health or nutritional supplement, the manufacturer can advertise the product after obtaining a unique identification number (UIN) from state licensing authorities[11].

10 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MjM1OQ

11 http://ayush.gov.in/event/prohibition-advertisements-ayurvedic-siddha-or-unani-drugs

Ban on online sales of medicines till next order: Delhi High Court

Recently, there was a huge debate going-on both at the state and center level regarding online sales of the medicine. E-Pharmacy a recent entrant in the e-commerce arena is receiving huge support from Central Government and investors. As per Ken Market Research's report[12], the total revenue generated by the online sales of healthcare products in India was INR 5,075.9 million in FY 2015 up from INR 771.0 million in FY 2012 at a CAGR of 87.4 during the period FY2012-FY2015. Though online pharmacy sector has shown tremendous growth in the economy and helped the public by providing them online portals where they can compare the price of the drugs, it has also increased the number of fraud cases in online sale of the prescription drugs.

Despite attaining a benchmark in the field of e-commerce, the sector is lacking in regulatory guidelines. The Drug & Cosmetic Act, 1940, governs the pharmacies in India. Since the law was written before the computer era, there are no laws related to internet and e-commerce. The Information Technology Act, 2000 (IT Act), governs all activities and issues related to the internet. But there is a lack of accurate and crystal clear laws and guidelines when it comes to e-pharmacies regulation. There is a need of stringent regulatory guidelines to be incorporated in current Drug & Cosmetic Act, 1940 (Act), to ensure efficient and legitimate running of e-pharmacies. Despite numerous oppositions from various physical Pharmacy associations over possibilities of misuse/fraudulence in online sales of medicines, the Central Drugs Standard Control Organization (CDSCO) on 28.08.2018, came up with draft rules on 'SALE OF DRUGS BY E-PHARMACY' with an aim to regulate e-pharmacy business and sales, storage and distribution therein across India under the Drugs and Cosmetics Rules, 1945 (Rules).

Ban on online sales

Recently Delhi High Court ordered[13] ban of the online medicines, which ban will continue till new laws are framed in this entity.

The bench comprising Chief Justice Rajendra Menon and Justice V K Rao said that "once the rules come into play, Online Pharmacies can start selling the medicines". The application for the impleadment was filed in a PIL by Zaheer Ahmed seeking a ban on "illegal" sale of drugs and medicines online. The main complaints in the PIL include[14]:

- Medicines worth lakhs was being sold online every day without much regulation and posing a huge risk to patients as well as doctors.
- Online sale of medicines is not permitted under the Act, and the Pharmacy Act
- The Drug Controller General of India, in 2015, had clearly directed all state drug controllers to protect the interest of public health by restraining such sale online.
- By allowing unchecked online sales, the government has failed in its responsibility to protect public health and fulfill its obligation.
- Drugs are different from common items; and their misuse and abuse can have serious consequences for public health.

12 https://www.kenresearch.com/healthcare/general-healthcare/india-online-healthcare-products-market-research-report/652-91.html

13 http://delhihighcourt.nic.in/dhcqrydisp_O.asp?pn=299654&yr=2018

14 https://economictimes.indiatimes.com/news/politics-and-nation/no-online-sale-of-medicines-till-norms-in-place-says-delhi-high-court/articleshow/67145977.cms.

- Internet is used by a large number of children, minors and also uneducated people in rural areas. They can become victims of wrong medication.
- Online pharmacies are working without drug licenses and are also indulging in selling psychotropic substances.

As per the petition filed - Online pharmacies are operating without a drug license and cannot be regulated in the present regime. Unregulated and unlicensed sale of medicines will increase risk of spurious, misbranded and sub-standard drugs being sold.

Conclusion

Delhi High Court ban on the sale of the online medicine will certainly give a direction to the authorities where they will need to come up with some stringent regulatory guidelines and fast-track the implementation process. This will not only regulate the online sale of medicine but will also help the e-pharma sector to have transparency with the drug authorities and abide with the regulatory guidelines for public safety.

CDSCO's safety guidelines for acne drug 'Isotretinoin'

On December 19, 2018, the Central Drugs Standard Control Organization (CDSCO) re-issued safety guidelines[15] for 'Isotretinoin' following public grievances related to drug's Adverse Drugs Reaction received at Centralized Public Grievance Redress and Monitoring System (CPGRAMS). Isotretinoin, is an oral drug used for the treatment and prevention of severe acne. The safety guidelines are published after consultation with Subject Expert Committee[16] (SEC), CDSCO, where the committee examined the risk/benefit profile of drug for the approved indications in the country, and recommended that the drug may cause severe birth defects during the course of treatment. Therefore, the CDSCO directed all the State and Union Territories' drugs controllers to inform manufacturer/distributer/retail chemists under their jurisdiction to comply with the following safety guidelines:

- The drug should be sold only on the prescription of a dermatologist.
- The patients should sign a consent form before undertaking the treatment.
- The Pack of the drug should carry box warning saying *"the drug may cause severe birth defect; you must not take this medicine if you are pregnant or may likely to become pregnant during treatment"*. It also mentions that "*You should also avoid pregnancy for 6 months after stopping the treatment"*.
- The manufacturers should provide a package insert along with their product in major local languages.
- The retail chemists should maintain the details of retail sale of the drug.

About Isotretinoin

Isotretinoin is a Retinoid, a naturally-occurring retinoic acid act and binds to the nuclear retinoic acid receptors (RARs), activated RARs serve as transcription factors that promote cell differentiation and apoptosis. This agent also exhibits immunomodulatory and anti-inflammatory responses and inhibits ornithine decarboxylase, thereby decreasing polyamine synthesis and keratinization. It is used as a topical dermatologic agent that is used in the treatment of ACNE VULGARIS and several other skin diseases[17].

Note - Isotretinoin capsules 10mg and 20 mg were approved by the CDSCO in June 2002 for cystic and conglobate acne, severe nodular acne unresponsive to antibiotic therapy with various conditions. The said approval also comprised with boxed warning for female patients that 'the drug may cause severe birth defect and patient should sign a consent form before undertaking treatment'. At present the drug is available in Indian market with various brand names like Acneone, Acnex-20, Across, Aktret, Ratino and Isopad.

15 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MjQxOQ==

16 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=MzQ=

17 https://pubchem.ncbi.nlm.nih.gov/compound/Isotretinoin#section=Top

Central Government bans the use of Buclizine as appetite stimulant

On December 13, 2018, the Central Government announced ban on the use of drug Buclizine (a *appetite stimulant*) which was found to be irrational for the human use. However, the drug will be available for marketing for the indications *"symptomatic treatment of various allergic conditions (rhinitis, conjunctivitis and urticaria) and for prevention and treatment of motion sickness"*[18].

Earlier, the Subject Expert Committee constituted by the Central Government examined the matter and stated that no clinical trial study report on human beings to justify the use of Buclizine as an appetite stimulant has been produced by the manufacturers and hence, the committee recommended to prohibit marketing of buclizine as an appetite stimulant. Later, the Drugs Technical Advisory Board also considered the said matter and recommended for prohibiting the manufacture, sale and distribution of Buclizine for the indication "as appetite stimulant".

Therefore, in exercise of the powers conferred by section 26A of the Drugs and Cosmetics Act (the 'Act'), and after examination of the recommendations of both; SEC and DTAB committee, the Central Government has banned Buclizine as an appetite stimulant and has made it necessary and expedient in public interest to regulate the manufacture, sale or distribution of Buclizine and its formulations for use in human beings; subject to the conditions that the manufacturer shall label the container of Buclizine and its formulation and also mention in conspicuous manner on the package insert and promotional literature of Buclizine and its formulation with the words "**Not to be used as appetite stimulant**". Section 26A is reproduced hereunder:

> ***Power of Central Government to prohibit manufacture, etc., of drug and cosmetic in public interest***.— *Without prejudice to any other provision contained in this Chapter, if the Central Government is satisfied, that the use of any drug or cosmetic is likely to involve any risk to human beings or animals or that any drug does not have the therapeutic value claimed or purported to be claimed for it or contains ingredients and in such quantity for which there is no therapeutic justification and that in the public interest it is necessary or expedient so to do, then, that Government may, by notification in the Official Gazette, regulate, restrict or prohibit the manufacture, sale or distribution of such drug or cosmetic.*

About Buclizine

Buclizine is a histamine H1 receptor antagonist from piperazine derivative family, has antiemetic and antivertigo activities primarily. Buclizine exerts its anti-emetic effect by binding to and blocking the muscarinic and histamine receptors in the vomiting center of the central nervous system (CNS). This may prevent activation of the chemoreceptor trigger zone (CTZ) and may reduce nausea and vomiting. Furthermore since buclizine possesses anti-cholinergic properties as well, the muscarinic receptors are similarly blocked[19].

Note – Buclizine is developed by Belgium-based UCB Pharma, which was acquired by India-based Mankind Pharma in year 2012. The Drug Controller General of India had approved this drug to sell as an appetite stimulant in 2006 and as an anti-allergic in 2010.

18 http://www.egazette.nic.in/WriteReadData/2018/193983.pdf

19 https://pubchem.ncbi.nlm.nih.gov/compound/Buclizine#section=Top

WHO launched a joint pilot project with USFDA to accelerate access to HIV medicines

The U.S. Food and Drug Administration (USFDA) and World Health Organization (WHO) have launched a joint pilot initiative to speed up approval of HIV medicines for supply to developing countries[20]. The FDA will share documents on HIV drug applications that have been approved or tentatively approved by the agency under the US President's Emergency Plan for AIDS Relief (PEPFAR) with WHO.

About Pilot Initiative

In the pilot, called the Collaborative Registration Procedure-Lite (CRP-Lite), the FDA will provide the WHO, Prequalification programme with reviews of HIV drug applications, initially for one or two medicines. WHO will then use the FDA's reviews to expedite its own assessments of the medicines, producing reviews which can then be shared with regulators in resource-limited countries to speed up their own regulatory review processes—making lifesaving drugs available to patients faster.

This pilot builds on the Collaborative Registration Procedure introduced by WHO in 2014, which has seen in-country registration times reduce from over two years to less than 90 days for over 300 products in 36 countries in Africa, Asia, the Caribbean and Eastern Europe.

These initiatives are important because most regulatory authorities in low-income countries are under-resourced and stretched, resulting in slow approvals of medicines that are desperately needed by patients.

About PEPFAR[21]

PEPFAR was launched in 2003 to address the global HIV/AIDS crisis by using U.S. funds to purchase, at low cost, antiretroviral therapies, including new combinations and formulations of medicines, for treatment in countries with limited resources that were hard-hit by the epidemic. Since 2004, the FDA has approved or tentatively approved 211 antiretroviral drug applications for use in PEPFAR partner countries and 193 of those are still available for treatment. The FDA-reviewed products are currently being used to treat over 14 million HIV patients globally (or about 38 percent of the total global population living with HIV). In addition, because of PEPFAR's ARV-supported programme to prevent mother-to-child transmission, more than 2.4 million babies have been born HIV-free who could have otherwise been infected.

20 https://www.who.int/medicines/news/2018/FDA-WHO-joint-pilot-to-accelerate-access-to-HIV-medicines/en/

21 https://www.who.int/medicines/news/2018/fda-who-access-to-medicines-accelerate.pdf

European Medicines Agency (EMA): Recommends approval of four medicines in its December meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended seven medicines for approval, including two orphan medicines at its December 2018 meeting[22].

A) The seven medicines recommended for approval are:

1. Besremi - for the treatment of polycythaemia vera without symptomatic splenomegaly.

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Besremi, intended for the treatment of polycythaemia vera without symptomatic splenomegaly. Besremi was designated as an orphan medicinal product on December 09, 2011.

Besremi will be available as a solution for injection (250 microgram/0.5 ml and 500 microgram /0.5 ml). The active substance of Besremi is ropeginterferon alfa-2b, which inhibits the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonises the action of growth factors and other cytokines involved in the development of myelofibrosis.

The applicant for Besremi is AOP Orphan Pharmaceuticals AG[23].

2. Lusutrombopag Shionogi - for the treatment of severe thrombocytopenia in adults with chronic liver disease undergoing invasive procedures.

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Lusutrombopag Shionogi, intended for the treatment of severe thrombocytopenia in adults with chronic liver disease undergoing invasive procedures.

Lusutrombopag Shionogi will be available as 3 mg film-coated tablets. The active substance of Lusutrombopag Shionogi is lusutrombopag, a thrombopoietin (TPO) receptor agonist. Lusutrombopag acts on the transmembrane domain of TPO receptors, to induce proliferation and differentiation of megakaryocyte progenitor cells, thus leading to thrombocytopoiesis.

The applicant for Lusutrombopag is Aeterna Shionogi B.V.[24]

3. Rizmoic - for the treatment of opioid-induced constipation.

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Rizmoic, intended for the treatment of opioid-induced constipation (OIC).

Rizmoic will be available as 200-microgram film-coated tablets. The active substance of Rizmoic is naldemedine, a peripherally-acting mu-opioid receptor antagonist which acts in tissues such as the gastrointestinal tract,

22 https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-10-13-december-2018

23 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-besremi_en.pdf

24 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-lusutrombopag-shionogi_en.pdf

thereby decreasing the constipating effects of opioids without reversing the central nervous system-mediated opioid effects.

The applicant for Silodosin is Shionogi B.V.[25]

4. Trecondi – for conditioning treatment prior to allogeneic Haematopoietic Stem Cell Transplantation (alloHSCT).

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Trecondi, intended for the conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT). Trecondi was designated as an orphan medicinal product on February 23, 2004.

Trecondi will be available as a 50 mg/ml powder for solution for injection/infusion. The active substance of Trecondi is treosulfan, a prodrug of an alkylating agent with cytotoxic activity against haematopoietic precursor cells.

The applicant for Trecondi is medac Gesellschaft fur klinische Spezialpraparate mbH[26].

5. Tobramycin PARI – Management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis.

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Tobramycin PARI, intended for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis.

Tobramycin PARI will be available as a 170 mg nebuliser solution. The active substance of Tobramycin PARI is tobramycin, an aminoglycoside antibiotic (ATC code: J01GB01) which primarily affects bacterial protein synthesis resulting in rapid concentration-dependent bacterial cell death.

The applicant for Tobramycin is PARI Pharma GmbH[27].

6. Zirabev – for treatment of carcinoma of the colon or rectum, breast cancer, non-small cell lung cancer, renal cell cancer and carcinoma of the cervix.

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Zirabev, intended for the treatment of carcinoma of the colon or rectum, breast cancer, non-small cell lung cancer, renal cell cancer and carcinoma of the cervix.

Zirabev will be available as a 25 mg/ml concentrate for solution for infusion. The active substance of Zirabev is bevacizumab, a monoclonal antibody which binds to vascular endothelial growth factor (VEGF), thereby inhibiting the binding of VEGF to its receptors on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

25 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-rizmoic_en.pdf

26 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-trecondi_en.pdf

27 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-tobramycin-pari_en.pdf

The applicant for Zirabev is Pfizer Europe MA EEIG[28].

7. Miglustat – for treatment of adult patients with mild to moderate type 1 Gaucher disease.

On December 13, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Miglustat Dipharma, intended for treatment of adult patients with mild to moderate type 1 Gaucher disease.

Miglustat Dipharma will be available as capsules (100 mg). The active substance of Miglustat Dipharma is miglustat, an inhibitor of glucosylceramide synthase, the enzyme responsible for the first step in the synthesis of glycosphingolipids. It works as substrate reduction therapy by reducing production of glycosphingolipids, the substrates of the defective enzyme in patients with type 1 Gaucher disease (glucocerebrosidase). Reducing glycosphingolipids levels is expected to slow down or prevent symptoms of type 1 Gaucher disease.

The applicant for Miglustat is Dipharma B.V.[29]

B) 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 six drugs via extensions of therapeutic indications as described in table (*New indication are marked in bold, and removed indication are marked in strikethrough*)

Sl.no.	Name of medicine	Full Indication	Marketing-authorisation holder
1	Adcetris (brentuximab vedotin)	**- Adcetris is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).** **- Adcetris is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT).** **-Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):** **following ASCT, or** **following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.** - Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). - Adcetris is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.	Takeda Pharma

28 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-zirabev_en.pdf

29 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-miglustat-dipharma_en.pdf

Sl.no.	Name of medicine	Full Indication	Marketing-authorisation holder
2	Rapiscan (regadenoson)	Rapiscan is a selective coronary vasodilator for use **in adults** as a pharmacological stress agent for: radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress. **the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated**.	GE Healthcare AS
3	Rubraca (rucaparib)	- **Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.** - Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.	Clovis Oncology UK Limited
4	Simponi (golimumab)	*Juvenile idiopathic arthritis* Polyarticular juvenile idiopathic arthritis (pJIA) Simponi in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children **2 years of age and older** ~~with a body weight of at least 40 kg~~, who have responded inadequately to previous therapy with MTX. In addition, the CHMP recommended approval of a new formulation of Simponi, a 45 mg/0.45 ml solution for injection in pre-filled pens, for the above indication.	Janssen Biologics B.V.
5	Sprycel (dasatinib)	Sprycel is indicated for the treatment of adult patients with: newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate. Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy. Sprycel is indicated for the treatment of paediatric patients with: newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. **newly diagnosed Ph+ ALL in combination with chemotherapy**.	Bristol-Myers Squibb Pharma EEIG
6	Trimbow (beclometasone dipropionate)	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 beta2-agonist **or a combination of a long-acting beta2-agonist and a long acting muscarinic antagonist.**	Chiesi Farmaceutici S.p.A

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 carries out a scientific assessment of the application and gives 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.

USFDA approves Sanofi's new pediatric vaccine for six diseases

On December 21, 2018, United States Food and Drug administration has approved VAXELIS™ (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine) indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to Haemophilus influenzae type b in children from 6 weeks through 4 years of age (prior to the 5th birthday)[30].

The approval also details the numerous warnings and risks that could possibly be associated with Vaxelis:

- VAXELIS is contraindicated in children with a history of severe allergic reaction (e.g., anaphylaxis) to a previous dose of VAXELIS, any ingredient of VAXELIS, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine, hepatitis B vaccine, or H. influenzae type b vaccine.
- Do not administer VAXELIS to anyone with a history of encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), within 7 days of a pertussis-containing vaccine, that is not attributable to another identifiable cause.
- Do not administer VAXELIS to anyone with a history of progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized.
- Vaccination with VAXELIS may not protect all individuals.
- Carefully consider benefits and risks before administering VAXELIS to persons with a history of:
    - fever of ≥40.5°C (≥105°F), hypotonic-hypo-responsive episode (HHE) or persistent, inconsolable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine.
    - seizures within 3 days after a previous pertussis-containing vaccine.
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following VAXELIS.

About VAXELIS

VAXELIS includes antigens for diphtheria, tetanus, pertussis (whooping cough), and poliomyelitis from Sanofi and antigens for H. influenzae type b and hepatitis B from MSD. VAXELIS is to be administered as a 3-dose series at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age. Three doses of VAXELIS constitute a primary immunization course against diphtheria, tetanus, H. influenzae type b invasive disease and poliomyelitis[31].

Note - VAXELIS was developed as part of a joint-partnership between Sanofi and MSD, known as Merck inside the United States and Canada. Both the companies are working on the production of VAXELIS to make it available in 2020 in U.S. market.

30 https://www.sanofipasteur.com/en/media-room/press-releases/FDA-Approves-VAXELIS-Sanofi-and-MSD-Pediatric-Hexavalent-Combination-Vaccine

31 https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM629109.pdf

USFDA approves two new treatments for rare blood diseases

On December 21, 2018, the United States Food and Drug Administration (USFDA) approved two new treatments Elzonris (tagraxofusp-erzs)[32] infusion and Ultomiris (ravulizumab)[33] injection for the treatment of rare blood diseases:

1. Elzonris (tagraxofusp-erzs) - for treatment of BPDCN

USFDA approved Elzonris (tagraxofusp-erzs) infusion for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients, two years of age and older. The FDA granted the approval of Elzonris to Stemline Therapeutics. The FDA also granted Breakthrough Therapy designation, Orphan Drug designation and Priority Review designation to Elzonris.

The efficacy of Elzonris was studied in two cohorts of patients in a single-arm clinical trial. The first trial cohort enrolled 13 patients with untreated BPDCN, and seven patients (54%) achieved complete remission (CR) or CR with a skin abnormality not indicative of active disease (CRc). The second cohort included 15 patients with relapsed or refractory BPDCN. One patient achieved CR and one patient achieved CRc.

About BPDCN

BPDCN is an aggressive and rare disease of the bone marrow and blood that can affect multiple organs, including the lymph nodes and the skin. It often presents as leukemia or evolves into acute leukemia. The disease is more common in men than women and in patients 60 years and older.

About ELZONRIS™

ELZONRIS, a CD123-directed cytotoxin, was granted full approval by the FDA for the treatment of adult and pediatric patients, two years and older with blastic plasmacytoid dendritic cell neoplasm (BPDCN), in treatment-naïve and previously-treated settings. In November 2018, the European Medicines Agency (EMA) granted ELZONRIS accelerated assessment for the upcoming marketing authorization application (MAA) submission, which is expected in the first quarter of 2019. ELZONRIS is also being evaluated in additional clinical trials in other indications including chronic myelomonocytic leukemia (CMML), myelofibrosis (MF) and other CD123 positive diseases[34].

2. Ultomiris (ravulizumab) - for treatment of PNH

The U.S. Food and Drug Administration approved Ultomiris (ravulizumab) injection for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH), a rare and life-threatening blood disease. The FDA granted the approval of Ultomiris to Alexion Pharmaceuticals. The FDA also granted Priority Review designation and Orphan Drug designation to Ultomiris.

Ultomiris is a long-acting complement inhibitor that prevents hemolysis. The efficacy of Ultomiris was studied in a clinical trial of 246 patients who previously had not been treated for PNH (treatment naïve), who were randomized to be treated with Ultomiris or eculizumab, the current standard of care for PNH. The results of the trial demonstrated that Ultomiris had similar results to eculizumab (non-inferior) – patients did not receive a transfusion and had similar incidence of hemolysis measured by the normalization of LDH levels in patients' blood (lactate dehydrogenase, or LDH, is an enzyme required during the process of turning sugar into energy in the body's cells). In addition, Ultomiris was studied in a second clinical trial of 195 patients with PNH who were

32 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629020.htm

33 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629022.htm

34 https://ir.stemline.com/news-releases/news-release-details/fda-approves-elzonristm-tagraxofusp-first-treatment-blastic

clinically stable after having been treated with eculizumab for at least the past six months. These patients were randomly selected to be treated with Ultomiris or to continue eculizumab. Ultomiris again demonstrated similar effects to eculizumab (non-inferior) based on several clinical measures including hemolysis and avoiding transfusion.

About PNH

PNH is a rare acquired disorder that leads to the rupture or destruction of red blood cells (hemolysis). Patients with PNH are missing a certain protein that normally protects red blood cells from being destroyed by the patient's immune system. Patients with PNH have sudden, recurring episodes where red blood cells are prematurely destroyed which may be triggered by stresses on the body, such as infections or physical exertion. During these episodes, the following symptoms may occur - severe anemia, profound fatigue, shortness of breath, and intermittent episodes of dark colored urine, kidney disease or recurrent pain. PNH can occur at any age, although it is most often diagnosed in young adulthood.

About ULTOMIRIS™

ULTOMIRIS™ (ravulizumab-cwvz) is the first and only long-acting C5 inhibitor administered every eight weeks that works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system that, when activated in an uncontrolled manner, plays a role in severe ultra-rare disorders like paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and anti-acetylcholine receptor (AchR) antibody-positive myasthenia gravis (MG). ULTOMIRIS is approved in the U.S. as a treatment for adults with PNH. Regulatory authorities in the European Union (EU) and Japan have accepted and are reviewing applications for the approval of ULTOMIRIS as a treatment for adults with PNH[35].

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35 https://news.alexion.com/press-release/product-news/alexion-receives-early-fda-approval-ultomiris-ravulizumab-cwvz-adults-par

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