EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Human medicines highlights 2018

Authorisation of new medicines

Key figures on the European Medicines Agency's (EMA) recommendations for the authorisation of new medicines in 2018:

84 Positive opinions

42 New active substances

5 Negative opinions

10 Withdrawn applications

3 Advanced therapy medicinal products

21 Orphan medicines

4 Accelerated assessments

1 Conditional marketing authorisations

3 Approval under exceptional circumstances

See more on the new recommendations from page 2.

Keeping medicines safe

Once a medicine has been put on the market, EMA and the EU Member States continuously monitor its quality and benefit/risk balance. Important new safety advice issued in 2018 included:

- Removal from the market of the multiple sclerosis treatments containing **daclizumab** (Zinbryta and Zenapax) due to serious and sometimes fatal cases of autoimmune encephalitis.
- Recommendation to suspend some **quinolone and fluoroquinolone antibiotics** and introduce changes including restrictions on the use of all others following a review of disabling and potentially permanent side effects reported with these medicines.
- Recommendation of new measures to avoid exposure of babies to **valproate medicines** in the womb because exposed babies are at high risk of malformations and developmental problems.
- Recommendation to restrict the use of **retinoid medicines** during pregnancy. The review confirmed that all oral retinoids can harm the unborn child.

See more on monitoring of medicines from page 6.

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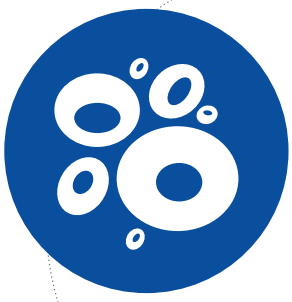
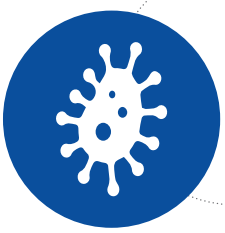
Medicines recommended for approval

Cancer



Alunbrig
Apealea
Braftovi
Carmustine Obvius
Erleada
Gefitinib Mylan
Imfinzi
Kanjinti
Kymriah ● ● ●
Lenalidomide Accord
Mektovi
Nerlynx
Ogivri
Pelgraz
Pemetrexed Krka
Poteligeo ●
Rubraca ● ●
Trazimera
Udenyca
Verzenios
Vyxeos ●
Yescarta ● ● ●
Zirabev

Infections



Alpivab
Biktarvy
Delstrigo
Fulphila
Juluca
Pelmeg
Pifeltro
Tobramycin PARI
Vabomere
Xerava
Ziextenzo

Neurology

Aimovig
Buvidal
Dzuveo
Emgality
Kigabeq
Namuscla ●
Onpattro ● ●
Rxulti
Slenyto
Tegsedi ● ●

Haematology/ Haemostaseology

Besremi ●
Cablivi ●
Deferiprone Lipomed
Hemlibra ●
Jivi ●
Lusutrombopag Shionogi
Mylotarg ●
Trecondi ●
Veyvondi ●

Immunology/ Rheumatology/ Transplantation

Duzallo
Halimatoz
Hefiya
Hulio
Hyrimoz
Ilumetri
Zessly

Endocrinology

Lamzede ● ●
Macimorelin Aeterna Zentaris
Mepsevii ● ●
Myalepta ● ●
Nityr
Semglee

Metabolism

Amglidia ●
Miglustat Dipharma
Segluromet
Steglatro
Steglujan

Pneumology/ Allergology

Bevespi Aerosphere
Riarify
Symkevi ●
Takhzyro ● ●
Trydonis

Vaccines

Dengvaxia
Flucelvax Tetra
Shingrix

Cardiovascular

Prasugrel Mylan

Hepatology/ Gastroenterology

Rizmoic

Ophthalmology

Luxturna ● ●

Reproductive medicine

Ulipristal Acetate Richter

Uro-nephrology

Silodosin Recordati

● Accelerated assessment ● Approval under exceptional circumstances ● ATMP ● Conditional marketing authorisation ● Orphan medicine ● PRIME

The medicines that contain a new active substance are highlighted in blue

These figures reflect EMA's recommendations which are sent to the European Commission for the adoption of an EU-wide marketing authorisation.
*This figure refers to medicines that had an orphan designation at the time of the Committee for Medicinal Products for Human Use (CHMP) opinion. At time of approval, orphan designations are reviewed by EMA's Committee for Orphan Medicinal Products (COMP) to determine whether the information available to date allows maintaining the medicine's orphan status.

OUTSTANDING CONTRIBUTIONS TO PUBLIC HEALTH

Advances in medicines authorisations are essential to advancing public health as they bring new opportunities to treat certain diseases. Below is a selection of medicines approved in 2018 that represent a significant progress in their therapeutic areas:

Advanced therapy medicinal products (ATMPs)

ATMPs are medicines based on genes, cells or tissues that offer ground-breaking new opportunities for the treatment of diseases. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate.

Cancer

Kymriah and **Yescarta**

the first two chimeric antigen receptors (CAR) T-cell therapies in the EU intended for the treatment of certain blood cancers. Kymriah and Yescarta are also the first medicines supported through EMA's PRIority MEdicines (PRIME) scheme that received a positive opinion from the CHMP.

Ophthalmology

Luxturna

for the treatment of adults and children with inherited retinal dystrophy caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness.

Medicines for children

EMA works to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately. Below is a non-exhaustive selection of medicines authorised for a paediatric indication in 2018:

Neurology

Kigabeq

a new paediatric-use marketing authorisation* (PUMA) for the treatment of infantile spasms (West's syndrome) and resistant partial epilepsy.

Slenyto

a new PUMA for the treatment of insomnia in children and adolescents with autism spectrum disorder or Smith-Magenis syndrome.

Metabolism

Amglidia

for the treatment of neonatal diabetes mellitus in newborns, infants and children.

Rare diseases

The EU framework for orphan medicines aims to encourage the development and marketing of medicines for patients with rare diseases by providing incentives for developers. Among the 84 medicines recommended for marketing authorisation in 2018, 21 had an orphan designation at the time of CHMP opinion. New orphan medicines with the potential to significantly benefit patients included:

Endocrinology

Lamzede

long-term enzyme replacement therapy in adults, adolescents and children with mild to moderate forms of alpha-mannosidosis.

Mepsevii

for the treatment of mucopolysaccharidosis type VII.

Neurology

Namuscla

for the treatment of myotonia in adult patients with non-dystrophic myotonic disorders. This is the first treatment for this disease to be authorised EU-wide.

*The paediatric-use marketing authorisation (PUMA) is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed exclusively for use in the paediatric population.

EARLY ACCESS TO MEDICINES THAT ADDRESS PUBLIC HEALTH NEEDS

Accelerated assessments

Four medicines received a recommendation for marketing authorisation following an accelerated assessment. This mechanism is reserved for medicines that are able to address unmet medical needs. It allows for faster assessment of eligible medicines by EMA's scientific committees (within a maximum of 150 days rather than 210 days).

Haematology/ Haemostaseology

Hemlibra

first-in-class medicine to prevent bleeding episodes in patients with haemophilia A who have factor VIII inhibitors.

Pneumology/Allergology

Takhzyro

first monoclonal antibody therapy for the prevention of recurrent attacks of hereditary angioedema.

Neurology

Onpattro

for the treatment of hereditary transthyretin-mediated amyloidosis.

Tegsedi

for the treatment of hereditary transthyretin amyloidosis.

Approval under exceptional circumstances

Three medicines were authorised under exceptional circumstances, a route that allows patients' access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because there are only very few patients with the disease, or the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorisation obligations and monitoring.

Endocrinology

Lamzede

for the treatment of patients with non-neurological manifestations of mild to moderate alpha-mannosidosis.

Post-authorisation obligations for the company include:

• Set up a patients registry to collect additional information on the long-term effectiveness and safety of treatment.

• Submit the results of a 24-month study in paediatric patients below 6 years of age.

Mepsevii

for the treatment of mucopolysaccharidosis type VII.

Post-authorisation obligations for the company include:

• Submit the results of a study based on adequate source of data deriving from a Disease Monitoring Program of patients with mucopolysaccharidosis VII.

Endocrinology

Myalepta

for the treatment of complications of leptin deficiency in patients with generalised or partial lipodystrophy which is often associated with severe metabolic abnormalities, including hypertriglyceridaemia, insulin resistance and/ or diabetes.

Post-authorisation obligations for the company include:

• Set up a patients registry to evaluate the long-term safety and effectiveness of the treatment.

• Conduct an efficacy study to further characterise the effect of the treatment on poor metabolic control once background therapy is maximised in patients with partial lipodystrophy.

• Provide an integrated immunogenicity report using validated assays for the detection of anti-drug antibodies from all available data to further investigate the clinical significance of the immunogenicity of the medicine.

Conditional marketing authorisation

One medicine received a recommendation for a conditional marketing authorisation, one of the possibilities in the EU to give patients early access to new medicines. As this medicine addresses an unmet medical need the conditional authorisation allows for early approval on the basis of less complete clinical data than normally required. This authorisation is subject to specific post-authorisation obligations to generate complete data on the medicine.

Cancer

Rubraca

for the treatment of relapsed or progressive ovarian cancer.

Post-authorisation obligations for the company include:

• Conduct a study to evaluate the efficacy and safety of the medicine in comparison with chemotherapy for the treatment of relapsed ovarian cancer.

NEW USES FOR EXISTING MEDICINES

65 extensions of indication were recommended in 2018. The extension of the use of a medicine that is already authorised for marketing in the EU can also offer new treatment opportunities for patients. Extensions of indication included:

Immunology/Rheumatology/Transplantation

Kineret

for the treatment of Still's disease in children and adults.

NEGATIVE OPINIONS

The Committee for Medical Products for Human Use (CHMP) adopted a negative opinion for five* medicines in 2018. When the Committee cannot reach an agreement on a positive benefit/risk, it issues a negative opinion on the marketing authorisation application and elaborates on the grounds. Applicants have the right to request a re-examination of the negative opinion within 15 days of receipt of the notification.

• EnCyzix
• Dexxience
• Eladynos
• Alsitek
• Exondys

*This figure does not include the initial negative opinion adopted by the CHMP on Nerlynx (neratinib) in February 2018. The applicant for this medicine requested re-examination of the Committee's negative opinion and, after considering the grounds for this request, the CHMP recommended granting a marketing authorisation for Nerlynx in June 2018.

Monitoring in real-life – optimising safe and effective use

Once a medicine has been put on the market, EMA and the EU Member States continuously monitor the quality and the benefit/risk balance of the medicine in the normal conditions of use after authorisation. This is to ensure that the medicine is given to patients in line with the approved conditions to achieve its full benefit and to protect them from any unwanted effects. Regulatory measures range from a change to the product information to the suspension or withdrawal of a medicine or recall of a limited number of batches.

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- Recommendation to suspend some **quinolone and fluoroquinolone antibiotics** and introduce changes including restrictions on the use of all others following a review of disabling and potentially permanent side effects reported with these medicines.
- Recommendation of new measures to avoid exposure of babies to **valproate medicines** in the womb, because exposed babies are at high risk of malformations and developmental problems.
- Recommendation to restrict the use of **retinoid medicines** during pregnancy. The review confirmed that all oral retinoids can harm the unborn child.
- Recommendation of new measures to minimise the risk of rare but serious liver injury with **Esmya** (ulipristal acetate), for the treatment of moderate to severe symptoms of uterine fibroids.
- New recommendation to restrict the use of **Keytruda** (pembrolizumab) and **Tecentriq** (atezolizumab) as first line-treatments for urothelial cancer (cancer of the bladder and urinary tract) in some patients with low levels of the protein PD-L1.
- Recommendation to restrict the use of **Xofigo** (radium-223 dichloride) to patients who have had two previous treatments for metastatic prostate cancer or who cannot receive other treatments, in view of the risk of early death and fractures in some patients.
- Warnings for the HIV treatment **dolutegravir** (Tivicay) about the possible risk of neural tube defects following exposure in very early pregnancy.
- Warnings for **fluoroquinolones antibiotics** about the rare risk of aortic aneurysm and dissection.
- Warning to healthcare professionals that **sildenafil** (Revatio, Viagra) is associated with an increased risk of pulmonary hypertension & death in infants exposed in utero in a clinical trial in growth retardation (off label).
- Warning to healthcare professionals that **rivaroxaban** (Xarelto) is associated with an increased mortality, bleeding and clots in patients treated in a clinical trial for trans-catheter aortic valve replacement (off label).
- Recommendation of new risk minimisation measures for **hydroxyethyl starch** (HES) solutions to protect patients at risk. Measures include training, controlled access and warning on the packaging.
- Recommendation to harmonise the maximum daily dose of the painkiller **metamizole** and the contraindications to its use in pregnancy or women who are breastfeeding. Marketed in many EU Member States, this medicine may occasionally cause severe side effects, such as effects on the blood.
- **Omega-3 fatty acid medicines** are not effective in preventing further heart and blood vessels problems in patients who have had a heart attack and will no longer be authorised for such use.

Ensuring integrity of clinical trial conduct and the manufacture and supply of medicines

Medicine development and manufacturing is global. It is important for regulators to ensure that EU standards are adhered to no matter where clinical trials or manufacturing takes place.

In 2018, EMA started a review of the blood pressure medicines candesartan, irbesartan, losartan, olmesartan and valsartan in relation to impurities found in some batches of these medicines. The impurities, N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), are classified as probable human carcinogens (substances that could cause cancer) based on animal studies.

The ongoing review is evaluating the root cause for the presence of these impurities, their possible impact on patients and what measures can be taken to reduce or eliminate these impurities from future batches. CHMP has also requested inspections of impacted manufacturing sites and sampling and testing of products from the EU market. Some medicines covered by this review have been recalled and are no longer available in the EU.

The CHMP adopted one negative opinion (refusing the granting of the marketing authorisation) for a medicine for which a GCP inspection reported non-compliance issues with the clinical study submitted.

10th medicine recommended for use outside the European Union

In 2018, EMA adopted a positive opinion for **Fexinidazole Winthrop** (fexinidazole), the first oral-only medicine for the treatment of human African trypanosomiasis, commonly known as sleeping sickness, due to *Trypanosoma brucei gambiense*. African trypanosomiasis is a life-threatening, neglected tropical disease that is endemic in sub-Saharan Africa. This medicine could potentially allow quicker and wider access to treatment in remote areas.

Fexinidazole Winthrop is the 10th medicine recommended by EMA under its Medicines for All programme. It is based on Article 58 of Regulation 726/2004, which allows the CHMP to assess a medicine in collaboration with the World Health Organization and its experts to give an opinion on its benefit-risk balance in situations where the intended use is in countries outside the EU.

NB: This document was updated on 16 January 2019 to correct two errors on page 2. Amglidia was erroneously labelled as new active substance, and Hemlibra, as orphan medicine. The overall figures did not change.

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