EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Human medicines highlights 2017

Authorisation of new medicines

Overview of the key figures on the European Medicines Agency's (EMA) recommendations for the authorisation of new medicines in 2017:

92 Positive opinions

35 New active substances

6 Negative opinions

14 Withdrawn applications

2 Advanced therapy medicinal products

19 Orphan medicines*

7 Accelerated assessments

3 Conditional marketing authorisations

2 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 2017 included:

- New warnings on the risk of lower limb amputation for patients who take the **SGLT2 inhibitors** canagliflozin, dapagliflozin and empaglifozin to treat type 2 diabetes.
- Restrictions of the use of **linear gadolinium contrast** agents in body scans because of deposition in the brain and other tissue.
- Restriction of the multiple sclerosis medicine **Zinbryta** because of the risk of severe liver damage.
- Suspension of modified-release **paracetamol medicines** because of the difficulty of managing overdose.

See more on monitoring of medicines from page 6.

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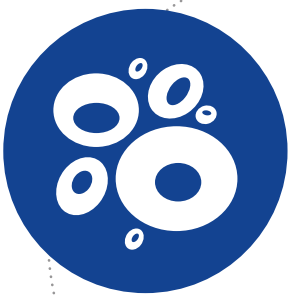
Medicines recommended for approval

Cancer



Axumin
Bavencio ● ●
Besponsa ●
Blitzima
Fotivda
Fulvestrant Mylan
Herzuma
Imatinib Teva B.V.
Kisqali
Lutathera ●
Mvasi
Ontruzant
Pemetrexed Hospira Limited
Qarziba (previously Dinutuximab beta Apeiron) ● ●
Ritemvia
Rixathon
Riximyo
Rydapt ●
Tecentriq
Tookad
Tuxella
Varuby
Zejula ●

Infections

Daptomycin Hospira
Darunavir Krka
Darunavir Krka d.d.
Efavirenz/Emtricitabine/Tenofovir disoproxil Krka
Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan
Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva
Emtricitabine/tenofovir disoproxil Krka d.d.
Entecavir Accord
Entecavir Mylan
Maviret ●
Prevymis ●
Ritonavir Mylan
Symtuza
Trumenba
Vosevi ●

Endocrinology

Alkindi
Crysvita ● ●
Insulin lispro Sanofi
Intrarosa
Ivabradine Accord
Miglustat Gen.Orph
Natpar ● ●
Nitisinone MendeliKABS
Ozempic
Ucedane
Xermelo ●
Yargesa

Immunology/ Rheumatology/ Transplantation

Amgevita
Cyltezo
Erelzi
Imraldi
Jylamvo 2mg/ml Oral Solution
Kevzara
Solymbic
Spherox ●
Tacforius
Tremyfa
Xeljanz

Neurology

Brineura ● ● ●
Lacosamide Accord
Mavenclad
Nyxoid
Ocrevus
Oxervate ● ●
Reagila
Spinraza ● ●
Verkazia ● ●
Zubsolv

Uro-nephrology

Elmiron ●
Lokelma
Tadalafil Lilly
Veltassa

Haematology/ Haemostaseology

Adynovi
Anagrelide Mylan
Refixia ●
VeraSeal

Pneumology/ Allergology

Elebrato Ellipta
Fasenra
Rolufta
Trelegy Ellipta
Trimbow

Dermatology

Dupixent
Kyntheum
Skilarence

Hepatology/ Gastroenterology

Jorveza ● ●
Alofisel ● ●

Metabolism

Cuprior ●
Febuxostat Mylan

Cardiovascular

Roteas

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

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 2017 that represent a significant improvement in their therapeutic areas:

Medicines for children

EMA works to ensure that medicines for use in children are ethically researched and authorised appropriately. 2017 marked the tenth anniversary of the EU Paediatric Regulation, which aims to stimulate the development of high quality, safe and effective medicines for children. New medicines approved in 2017 include:

Neurology

Brineura

for the treatment of a very rare, fatal neurodegenerative condition in children called neuronal ceroid lipofuscinosis type 2 (CLN2) disease. This is the first medicine approved in the EU for the treatment of CLN2, which will bring an outstanding benefit to patients.

Spinraza

to treat spinal muscular atrophy (SMA), an inherited disease usually diagnosed in the first year of life that affects the motor neurons. This is the first medicine approved in the EU for the treatment of SMA, which will bring an outstanding benefit to patients.

Endocrinology

Alkindi

for the treatment of primary adrenal insufficiency, a rare hormonal disorder in infants, children and adolescents.

Crysvita

for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children and adolescents with growing skeletons.

Advanced therapy medicinal products (ATMPs)

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

Rheumatology/ Transplantation

Spherox

to treat adult patients who have symptomatic articular cartilage defects in the knee.

Gastroenterology

Alofisel

for the treatment of complex perianal fistulas in patients with Crohn's disease.

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 92 medicines recommended for marketing authorisation, 19 had an orphan designation at the time of CHMP opinion in 2017. New orphan medicines with the potential to significantly benefit patients included:

Neurology

Oxervate

for the treatment of neurotrophic keratitis, a rare eye disease.

Cancer

Qarziba

(previously Dinutuximab beta Apeiron) for the treatment of high-risk neuroblastoma.

Endocrinology

Xermelo

for the treatment of carcinoid syndrome.

EARLY ACCESS TO MEDICINES THAT ADDRESS PUBLIC HEALTH NEEDS

Accelerated assessments

Seven 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 up to 150 days rather than up to 210 days).

Neurology

Brineura

to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease.

Oxervate

for the treatment of moderate to severe neurotrophic keratitis.

Spinraza

to treat patients with spinal muscular atrophy.

Verkazia

to treat severe vernal keratoconjunctivitis in children and adolescents.

Infections

Maviret

for the treatment of chronic hepatitis C virus (HCV) infection.

Vosevi

for the treatment of chronic hepatitis C virus (HCV) infection.

Gastroenterology

Jorveza

to treat eosinophilic esophagitis, a rare inflammatory condition of the oesophagus.

Conditional marketing authorisations

Three medicines received a recommendation for a conditional marketing authorisation, one of the possibilities in the EU to give patients early access to new medicines. This tool allows for the early approval of a medicine on the basis of less complete clinical data than normally required if the medicine addresses an urgent unmet medical need. These medicines are subject to specific post-authorisation obligations for medicine developers to obtain complete data on the medicine.

Endocrinology

Natpar

treatment for patients with chronic hypoparathyroidism who cannot be adequately controlled with standard treatment with calcium and vitamin D.

Post-authorisation obligations:

The company will conduct a further study to confirm the benefits an d risks of the medicine and the appropriateness of the once-a-day dosing schedule.

Crysvita

treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children and adolescents with growing skeletons.

Post-authorisation obligations:

The company will:

• Provide updated results from two ongoing studies in children aged between 5 and 12 years and between 1 and 4 years.

• Conduct and submit the results of a study comparing Crysvita with oral phosphate and active vitamin D in children with X-linked hypophosphataemia.

Cancer

Bavencio

treatment of metastatic Merkel cell carcinoma.

Post-authorisation obligations:

The company will provide further data from the ongoing study of patients who did not receive chemotherapy before starting treatment with Bavencio.

Approval under exceptional circumstances

Two 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.

Cancer

Qarziba

(previously Dinutuximab beta Apeiron) - for the treatment of high-risk neuroblastoma.

Post-authorisation obligations:

The company will:

- Monitor the safety of the medicine using a patient registry and provide yearly updates.
- Perform tests to obtain more information on how the medicine is processed by the body and how the immune system responds to the medicine.
- Provide the results of a study looking at the effect of giving Qarziba together with interleukin-2.
- Report on the 5-year survival rates of patients who took part in studies.

Neurology

Brineura

to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease.

Post-authorisation obligations:

The company will provide further data from studies on the safety of Brineura, including the risk of allergic reactions when used long-term, and on its long-term effectiveness in delaying or stopping worsening of movement and language skills. The studies will include children below 2 years of age, for whom there are currently no data.

NEW USES FOR EXISTING MEDICINES

51 extensions of indication were recommended in 2017. The extension of the use of a medicine that is already approved in a new therapeutic indication can also offer new treatment opportunities for patients. Extensions of indication included:

Neurology

Soliris

For the treatment of refractory generalised myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive.

Infections

Truvada

For the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first-line agents.

NEGATIVE OPINIONS

The Committee for Medical Products for Human Use (CHMP) adopted a negative opinion for six medicines in 2017. When the Committee cannot reach an agreement on a positive benefit/risk, it issues a negative opinion on the marketing authorisation 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.

- Adlumiz
- Aplidin*
- Fanaptum
- Human IGG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech
- Masipro
- Onzeald

*The company that markets Aplidin has requested a re-examination of the CHMP's December 2017 opinion. Upon receipt of the grounds of the request, the CHMP will re-examine its opinion and issue a final recommendation.

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. At the same time, patients are protected 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.

Important new safety advice issued in 2017 included:

- Information about a potential increased risk of lower limb amputation (mostly affecting the toes) in patients taking the **SGLT2 inhibitors** canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes.

- Recommendations to restrict the use of some **linear gadolinium agents** used in MRI body scans and suspend the authorisations of others. EMA's scientific review found that small amounts of gadolinium may remain in the brain after a scan with these agents, although there is currently no evidence that these small amounts cause any harm.

- Recommendation to restrict the use of the multiple sclerosis medicine **Zinbryta** in view of the risk of serious liver damage in some patients.

- Recommendation to suspend marketing of **paracetamol medicines** designed to release the active ingredient over a long period (modified-release medicines) because of the difficulty in managing overdoses.

- New recommendation on medicines containing a combination **of dienogest 2 mg and ethinylestradiol 0.03 mg** which can continue to be used to treat moderate acne when certain other treatments have failed, but should only be used in women who also choose oral contraception.

- Prescribing information for the antibiotic **vancomycin** to be changed to ensure appropriate use in the treatment of serious infections caused by Gram-positive bacteria. The recommendation aims to ensure appropriate use in the context of the fight against antimicrobial resistance.

- New contraindication for **Uptravi**, which must not be taken at the same time as medicines, such as gemfibrozil, that are strong blockers (inhibitors) of the liver enzyme CYP2C8.

- New recommendation for **Symbioflor 2** to continue to be used to treat irritable bowel syndrome (IBS), but not for other functional gastrointestinal disorders. The company will provide a study on effectiveness and safety among patients with different features of IBS.

- Review of human **factor VIII medicines** authorised in the EU: EMA concluded that there is no clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines. Patients should therefore continue to use their factor VIII medicines as prescribed by the doctor.

- New contraception recommendations for male patients regarding concerns that **mycophenolate medicines** (used to prevent rejection of transplanted organs) cause miscarriages or birth defects.

- New recommendation on injectable **methylprednisolone medicines** containing lactose (used to treat the symptoms of severe allergic reactions) which must not be used in patients with a known or suspected allergy to the proteins in cows' milk.

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 2017, two centralised marketing authorisation applications were withdrawn as a result of non-compliance with EU good manufacturing practice (GMP) and one as a result of good clinical practice (GCP) non-compliance.

Seven batches of Zoledronic acid were recalled from hospitals, pharmacies and wholesalers in six EU Member States following sampling from the EU market and testing by an Official Medicines Control Laboratory as part of the Agency's routine market surveillance programme. A subsequent GMP inspection of the manufacturer verified that the cause of the problem was limited to the batches in question and that appropriate corrective actions were implemented.

The CHMP adopted two negative opinions (refusing the granting of the marketing authorisation) for medicines for which GCP inspections reported non-compliance issues with the clinical studies submitted.

GCP inspections of two sites of a contract research organisation (CRO) led to a European review of the impact of the findings. As an outcome of the review the CHMP recommended the suspension of a number of nationally authorised medicines for which bioequivalence studies were conducted by the two concerned CRO sites.

Public hearing on valproate

On 26 September, EMA organised its first public hearing at its premises in London. A total of 65 citizens - including patients, carers, doctors, pharmacists and academia - participated in the event and shared their experience with valproate, a medicine that treats epilepsy, bipolar disorder and migraine.

The public hearing is part of an ongoing review of the safety of using valproate-containing medicines in women and girls who are pregnant or of childbearing age by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC). There is a risk of malformations and neurodevelopmental problems in babies who are exposed to valproate in the womb. At the end of this review, EMA will publish an assessment report on measures to reduce this risk.