EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Human Medicines Highlights 2022

An agency of the European Union

AUTHORISATION OF NEW MEDICINES

Key figures[1] on the European Medicines Agency's (EMA) recommendations for the authorisation of new medicines in 2022:

89
Positive opinions

41
New active substances

3
Negative opinions

16
Withdrawn applications

PRIME	Advanced therapy medicinal products	Orphan medicines[2]	Accelerated assessments	Conditional marketing authorisations	Approvals under exceptional circumstances	Biosimilars
8	**6**	**21**	**5**	**9**	**5**	**8**

KEEPING PATIENTS SAFE

Once a medicine has been put on the market, EMA and the European Union (EU) Member States continuously monitor its quality and benefit/risk balance.

In 2022, the product information for **467 centrally authorised medicines** was updated on the basis of new safety data. The revised information helps patients and healthcare professionals make informed decisions when using or prescribing a specific medicine.

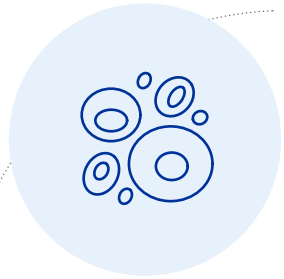
See page 14 for important new safety advice issued in 2022.

[1] These figures reflect EMA's recommendations which are sent to the European Commission for the adoption of an EU-wide marketing authorisation.

[2] This figure refers to medicines that had their orphan designation confirmed by 31 December 2022. At the 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.

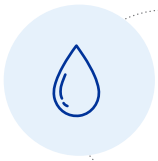
MEDICINES RECOMMENDED FOR APPROVAL

Cancer



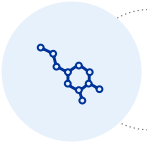
Breyanzi
Camcevi
Carvykti
Celdoxome pegylated liposomal
Ebvallo
Imjudo
Kimmtrak
Lunsumio
Opdualag
Orgovyx
Pemetrexed Baxter
Pepaxti
Plerixafor Accord
Pluvicto
Scemblix
Sorafenib Accord
Tabrecta
Tecvayli
Thalidomide Lipomed
Tremelimumab AstraZeneca
Vegzelma
Zolsketil pegylated liposomal
Zynlonta

Haematology/ Haemostaseology



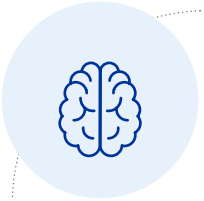
Cevenfacta
Dasatinib Accord
Dasatinib Accordpharma
Hemgenix
Roctavian
Stimufend

Metabolism



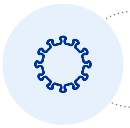
Amversio
Nulibry
Pyrukynd
Xenpozyme
Zokinvy

Neurology



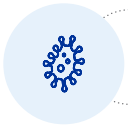
Amifampridine SERB
Amvuttra
Dimethyl fumarate Mylan
Dimethyl fumarate Neuraxpharm
Dimethyl fumarate Polpharma
Dimethyl fumarate Teva
Melatonin Neurim
Quviviq
Rayvow
Sugammadex Amomed
Sugammadex Fresenius Kabi
Upstaza
Vydura
Vyvgart

Covid-19



Evusheld
Paxlovid
COVID-19 Vaccine Valneva
VidPrevtyn Beta

Infections

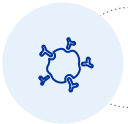


Beyfortus
Ertapenem SUN
Livtencity
Sunlenca

Endocrinology

Eladynos
Inpremzia
Kauliv
Mounjaro
Mycapssa
Pombiliti
Sitagliptin Accord
Sitagliptin / Metformin hydrochloride Accord
Sondelbay
Teriparatide SUN
Truvelog Mix 30
Vildagliptin / Metformin hydrochloride Accord

Immunology/Rheumatology/ Transplantation



Dimethyl fumarate Accord
Enjaymo
Teriflunomide Accord
Teriflunomide Mylan

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

Medicines that contain a new active substance are highlighted in bold

MEDICINES RECOMMENDED FOR APPROVAL

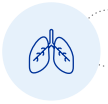
Nephrology

Kapruvia
Lupkynis
Kinpeygo ● ●

Ophthalmology

Ranivisio ●
Vabysmo
Ximluci ●

Pneumology/ Allergology



Pirfenidone axunio
Pirfenidone Viatris
Tezspire

Dermatology

Filsuvez ●
Spevigo ●

Diagnostic agents

Illuzyce
Locametz

Vaccines

PreHevbri
Qdenga

Gastroenterology/ Hepatology

Livmarli ● ●

Reproductive

Ganirelix Gedeon Richter

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

Medicines that contain a new active substance are highlighted in bold

IMPORTANT CONTRIBUTIONS TO PUBLIC HEALTH

Authorisation of new medicines is essential to advancing public health as they bring new opportunities to treat certain diseases. Below is a selection of medicines approved in 2022 that represent significant progress in their therapeutic areas[3]:

Cancer

Carvykti

for the treatment of adults with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since they received their last treatment.

Ebvallo

for the treatment of a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease. This medicine is intended for adults and children who develop this malignancy after receiving an organ- or a bone marrow-transplantation.

Kimmtrak

a monotherapy for treatment of adult patients with a form of eye cancer called uveal melanoma.

Haematology

Breyanzi

a gene therapy for the treatment of adults with three subtypes of non-Hodgkin lymphoma (diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B)), whose cancer has come back or who have not responded to treatment after two or more lines of systemic therapy.

Hemgenix

the first gene therapy for the treatment of severe and moderately severe haemophilia B, an inherited disorder characterised by an increased bleeding tendency due to a partial or complete deficiency in the activity of factor IX.

Haematology

Roctavian

for the treatment of severe haemophilia A in adults who do not have factor VIII inhibitors (auto-antibodies which make factor VIII medicines less effective) and no antibodies to adeno-associated virus serotype 5 (AAV5).

Metabolism

Mounjaro

a first-in-class medicine that activates both the GLP-1 and GIP receptors, leading to improved blood sugar control in patients with type II diabetes.

Xenpozyme

the first therapy for the treatment of acid sphingomyelinase deficiency (ASMD), a rare genetic condition, historically known as Niemann-Pick disease type A, A/B and B.

Zokinvy

the first treatment for children with progeroid syndromes, an ultra-rare genetic disease which causes premature aging and death.

Neurology

Upstaza

the first treatment for adults and children with aromatic L amino acid decarboxylase (AADC) deficiency, an ultra-rare genetic disorder affecting the nervous system.

Pneumology/ Allergology

Beyfortus

the first medicine for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in newborns and infants during their first RSV season (when there is a risk of RSV infection in the community).

[3] Vaccines and therapeutics to treat COVID-19 are listed on pages 5 and 7, respectively.

Highlights on Public Health Emergencies of International Concern

EMA is contributing to tackling the COVID-19 and mpox[4] pandemics by expediting the development and approval of safe and effective treatments and vaccines. This includes the reduction of timelines for evaluation to less than 150 working days and the use of rolling reviews.

The Agency also provides comprehensive and science-based information to patients and healthcare professionals.

COVID-19

Vaccines

February

Comirnaty, booster in adolescents from 12 years of age

Spikevax, primary vaccination in children from 6 to 11 years of age

May

Vaxzevria, booster in adults

June

Nuvaxovid, primary vaccination in 12 to 17-year-olds

COVID-19 Vaccine Valneva, primary vaccination in adults from 18 to 50 years of age

VidPrevtyn Beta, booster in adults from 18 to 50 years of age

July

Spikevax, booster in adolescents from 12 to 17 years of age

September

Comirnaty, booster in children from 5 to 11 years of age

Comirnaty, Original/Omicron BA.1 adapted booster in people from 12 years of age

Comirnaty, Original/Omicron BA.4-5 adapted booster in people from 12 years of age

Spikevax, Bivalent Original/Omicron BA.1 adapted booster in people from 12 years of age

Nuvaxovid, booster in adults

October

Comirnaty, primary vaccination in young children aged 6 months to 4 years

Spikevax, primary vaccination in young children aged 6 months to 5 years

Spikevax, Bivalent Original/Omicron BA.4-5 adapted booster in people from 12 years of age

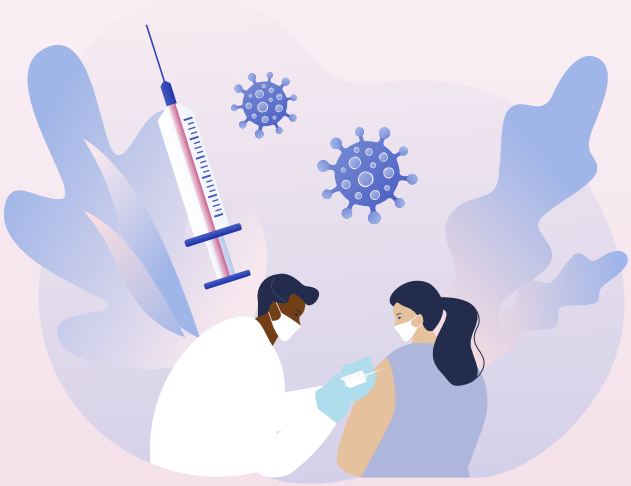
November

Comirnaty, Original/Omicron BA.4-5 adapted booster in children aged 5 to 11 years

December

Spikevax, booster in children from 5 to 11 years of age

Spikevax, Bivalent Original/Omicron BA.1 adapted booster in children aged 6 to 11 years



[4] In November 2022, the World Health Organization (WHO) recommended to use 'mpox' as synonym for monkeypox disease after a global outbreak of the disease in early 2022.

The overview below summarises the characteristics of the COVID-19 vaccines authorised in the EU (as of December 2022):

Overview of authorised COVID-19 vaccines

Vaccine	Platform	Strain	Use	Population ≥6 months	Population ≥5 years	Population ≥12 years	Population ≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	Primary vaccination	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
			Booster		✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted)	Booster			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted)	Booster		✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	Primary vaccination	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
			Booster		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted)	Booster		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.4-5 variants (adapted)	Booster			✓	✓
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Jcovden (Janssen)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Nuvaxovid (Novavax)	Protein	Original strain	Primary vaccination			✓	✓
			Booster				✓
COVID-19 Vaccine Valneva (Valneva)	Inactivated	Original strain	Primary vaccination				✓ 18-50 years
VidPrevtyn Beta (Sanofi Pasteur)	Protein	Beta variant	Booster				✓

Safety updates

EMA's safety committee (PRAC) issued monthly updates on the safety of every authorised COVID-19 vaccine reflecting data collected and assessed since the vaccine's authorisation. For details on the safety information of each vaccine, please see Safety of COVID-19 vaccines.

International collaboration

Under the OPEN framework EMA invited international regulators from Australia, Canada, Japan, Switzerland and the World Health Organization (WHO) to particpate in the review of all COVID-19 vaccines and therapeutics.

EMA's assessments are also used to support the World Health Organization's Emergency Use Listing of COVID-19 vaccines, a risk-based procedure for assessing and listing vaccines to expedite their availability to people affected by a public health emergency. EMA is the regulatory authority of record for the following licensed and unlicensed vaccines: Comirnaty, Vaxzevria, Jcovden, Spikevax, Nuvaxovid, VidPrevtyn, HIPRA, Valneva and Curevac.

Emergency Task Force recommendations

In January, EMA's Emergency Task Force (ETF) highlighted the growing evidence indicating that mRNA COVID-19 vaccines do not cause pregnancy complications for expectant mothers and their babies. The task force undertook a detailed review of several studies involving around 65,000 pregnancies at different stages.

In December, the ETF concluded that bivalent original/Omicron BA.4-5 mRNA vaccines may be used for primary vaccination in children and adults, in addition to their approved use as boosters[5]. Further clinical research and observational studies are expected to provide additional information on the safety and effectiveness of the bivalent vaccines for primary vaccination.

Manufacturing

Throughout 2022, EMA continued to approve additional manufacturing capacity for COVID-19 vaccines, from 52 manufacturing sites approved in 2021 to 68 manufacturing sites in 2022. EMA further supported shelf-life extensions for some COVID-19 vaccines and therapeutics.

Therapeutics

January

Paxlovid, to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

March

Evusheld, for the prevention of COVID-19 in adults and adolescents from 12 years of age weighing at least 40 kg before potential exposure to the SARS-CoV-2 virus.

September

Evusheld, extension of indication to include treatment of adults and adolescents with COVID-19 who do not require supplemental oxygen.

Veklury, extensions of indication to include children at least 4 weeks old and weighing at least 3 kg with pneumonia requiring supplemental oxygen or other non-invasive ventilation at the start of treatment, and children weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

[5] The ETF's statement was issued in the context of its public health emergency response activities. It does not reflect a change to the product information of the authorised vaccines.

Effectiveness of monoclonal antibodies against emerging strains of SARS-CoV-2

In December, the ETF warned that monoclonal antibodies that attach to the spike protein of SARS-CoV-2 may not be effective against emerging strains of the virus.

Healthcare professionals will need to consider alternative treatments, especially if subvariants such as BQ.1 and BQ.1.1 become prevalent. Antiviral treatments such as Paxlovid (nirmatrelvir/ ritonavir) and Veklury (remdesivir), which have different mechanisms of action, are expected to retain their activity against the emerging strains.

MPOX / MONKEYPOX

An atypical outbreak of mpox (monkeypox) was declared in Europe in May 2022, following reports of a number of cases in several Member States not linked to countries where the disease is endemic. The WHO subsequently declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC) on 23 July 2022.

In June, EMA's Emergency Task Force (ETF) recommended that **Jynneos**, a vaccine against mpox available in the United States, can be used to prevent mpox while supplies in the EU remain limited. National authorities may decide to import Jynneos as a temporary measure.

In July, the CHMP recommended an extension of the use of the smallpox vaccine **Imvanex** (live modified vaccinia virus Ankara) to include protecting adults from mpox and disease caused by vaccinia virus.

EMA also published advice issued by its ETF on the intradermal use of Imvanex / Jynneos against mpox. National authorities may decide as a temporary measure to use Imvanex as an intradermal injection at a lower dose to protect at-risk individuals during the current mpox outbreak while supply of the vaccine remains limited.

THREE MEDICINES RECOMMENDED FOR USE OUTSIDE THE EUROPEAN UNION

In April 2022, the CHMP adopted a positive opinion for two diabetes mellitus treatments, **Actrapid** (insulin human) and **Insulatard** (insulin human), for use outside the EU. Both insulins have been centrally authorised in the EU since 2002 and must be stored in a refrigerator (2–8°C). These strict storage conditions are difficult to adhere to in some countries outside the EU.

Following the evaluation of new stability data, the CHMP concluded that both products can be stored at temperatures up to 30°C for up to four weeks before they are used or carried as a spare. The CHMP opinion paves the way towards increased access to treatment for diabetes patients worldwide.

In October 2022, the CHMP adopted a positive opinion for Dengue Tetravalent Vaccine (live, attenuated) Takeda for the prevention of fever, severe disease and hospitalisation caused by dengue virus serotypes 1, 2, 3 and 4 in people from four years of age. Dengue is a mosquito-borne tropical disease caused by the dengue virus, leading to an estimated 20,000 to 25,000 deaths per year.

With Actrapid, Insulatard and Dengue Tetravalent Vaccine Takeda, EMA has recommended a total of 15 medicines under EU Medicines for all (EU-M4All), a mechanism that allows the CHMP to assess and give opinions on medicines that are intended for use in countries outside the EU under Article 58 of Regulation (EC) No 726/2004.

EARLY ACCESS TO MEDICINES THAT ADDRESS PUBLIC HEALTH NEEDS

Accelerated assessments

Five[6] 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).

Cancer

Kimmtrak

a monotherapy for the treatment of adult patients with a form of eye cancer called uveal melanoma.

Lunsumio

for the treatment of relapsed or refractory follicular lymphoma, a cancer of lymphocytes, white blood cells involved in the body's defences.

Tecvayli

for the treatment of adults with relapsed and refractory multiple myeloma who have received at least three prior therapies.

Infections

Beyfortus

for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in newborns and infants during their first RSV season (when there is a risk of RSV infection in the community).

Metabolism

Xenpozyme

for the treatment of patients with acid sphingomyelinase deficiency (ASMD), a rare genetic condition, historically known as Niemann-Pick disease type A, A/B and B. Xenpoxyme is the first ASMD-specific treatment.

[6] Treatments and vaccines for COVID-19 are not included in this figure as they followed a specific accelerated timetable for COVID-19 related medicines.

Conditional marketing authorisations

Nine medicines received a recommendation for a conditional marketing authorisation, one of the possibilities in the EU to give patients early access to new medicines. As these medicines address unmet medical needs the conditional authorisation allows for early approval on the basis of less complete clinical data than normally required (products for use in emergency situations may have less complete pharmaceutical or non-clinical data). These authorisations are subject to specific post-authorisation obligations to generate complete data on the medicines.

Cancer

Carvykti

for the treatment of adults with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since they received their last treatment.

Lunsumio

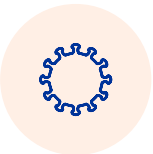
for the treatment of relapsed or refractory follicular lymphoma, a cancer of lymphocytes, white blood cells involved in the body's defences.

Tecvayli

for the treatment of adults with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since receiving the last treatment.

Zynlonta

for the treatment of adult patients with diffuse large B-cell lymphoma and high-grade B-cell lymphoma.



COVID-19

Paxlovid

to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Dermatology

Spevigo

for the treatment of flares in adult patients with generalised pustular psoriasis, a skin disorder that consists of pus spots surrounded by areas of red skin.

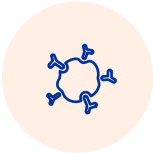
Haematology / Haemostaseology

Hemgenix

the first gene therapy for the treatment of severe and moderately severe haemophilia B, an inherited disorder characterised by an increased bleeding tendency due to a partial or complete deficiency in the activity of factor IX.

Roctavian

the first gene therapy to treat severe haemophilia A, a rare inherited bleeding disorder caused by lack of factor VIII.



Immunology / Rheumatology / Transplantation

Kinpeygo

for the treatment of adults with primary immunoglobulin A (IgA) nephropathy, a kidney disease that occurs when the antibody IgA builds up in the kidneys.

Approval under exceptional circumstances

Five 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

Ebvallo

for the treatment of a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease. This medicine is intended for adults and children who develop this malignancy after receiving an organ- or a bone marrow-transplantation.

Dermatology

Livmarli

for the treatment of cholestatic pruritus (itching) in adult and paediatric patients from two months of age with Alagille syndrome, an inherited condition in which bile builds up in the liver.

Metabolism

Zokinvy

the first treatment for children with progeroid syndromes, an ultra-rare genetic disease which causes premature aging and death.

Nulibry

for the treatment of molybdenum cofactor deficiency type A, an ultra-rare condition that appears shortly after birth and leads to brain injury and death.

Neurology

Upstaza

the first treatment for adults and children with aromatic L amino acid decarboxylase (AADC) deficiency, an ultra-rare genetic disorder affecting the nervous system.

Priority medicines (PRIME)

The enhanced development support provided by PRIME aims at helping patients to benefit as early as possible from promising medicines that target an unmet medical need, by optimising the generation of robust data and enabling accelerated assessment. This year, eight PRIME-designated medicines were recommended for approval (Beyfortus, Breyanzi, Carvykti, Ebvallo, Hemgenix, Roctavian, Tecvayli, Xenpozyme).

Thirteen medicines under development were included in the scheme in 2022, pertaining to the following disease areas:

- Endocrinology-Gynaecology-Fertility-Metabolism (2)
- Neurology (2)
- Oncology (2)
- Vaccines (2)
- Haematology–Haemostaseology (1)
- Infectious diseases (1)
- Musculoskeletal and connective tissue disorders (1)
- Ophthalmology (1)
- Uro-nephrology (1)

MEDICINES FOR 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.

Orphan designations are reviewed by EMA's Committee for Orphan Medicinal Products (COMP) at the time of approval to determine whether the information available to date allows maintaining the medicine's orphan status and granting the medicine ten years of market exclusivity. In 2022, 21 medicines had their orphan designation confirmed by the end of the year.

New orphan medicines with the potential to significantly benefit patients for which there are no other approved products included:

Cancer

Carvykti

for the treatment of adults with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since they received their last treatment.

Ebvallo

for the treatment of a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease. This medicine is intended for adults and children who develop this malignancy after receiving an organ- or a bone marrow-transplantation.

Kimmtrak

a monotherapy for the treatment of adult patients with a form of eye cancer called uveal melanoma.

Haematology / Haemostaseology

Hemgenix

the first gene therapy for the treatment of severe and moderately severe haemophilia B, an inherited disorder characterised by an increased bleeding tendency due to a partial or complete deficiency in the activity of factor IX.

Haematology / Haemostaseology

Roctavian

for the treatment of severe haemophilia A in adults who do not have factor VIII inhibitors (auto-antibodies produced by the immune system which make factor VIII medicines less effective) and no antibodies to adeno-associated virus serotype 5 (AAV5).

Metabolism

Xenpozyme

for the treatment of two types of Niemann-Pick disease, a rare metabolic disorder caused by acid sphingomyelinase deficiency (ASMD). Xenpoxyme is the first ASMD-specific treatment.

Zokinvy

the first treatment for children with progeroid syndromes, an ultra-rare genetic disease which causes premature aging and death.

NEW USES FOR EXISTING MEDICINES

90 extensions of indication were recommended in 2022, including 37 for paediatric use[7]. 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[8] included:

Cardiovascular

Jardiance

for the treatment of all types of heart failure, including those with preserved ejection fraction.

Adcirca

for the treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years and above.

Gastroenterology/ Hepatology

Dupixent

for the treatment of eosinophilic esophagitis (a rare, chronic, inflammatory disease of the esophagus) in adults and adolescents 12 years and older who cannot follow conventional medicinal therapy.

Infections

Xydalba

for the treatment of acute bacterial skin and skin structure infections in adults and paediatric patients aged 3 months and older.

Immunology / Rheumatology / Transplantation

Jakavi

for the treatment of paediatric patients with acute and chronic Graft vs Host Disease (when white blood T cells in donated stem cells or bone marrow attack the host's body cells) from 12 years of age, who have inadequate response to corticosteroids or other systemic therapies.

NEGATIVE OPINIONS

The Committee for Medical Products for Human Use (CHMP) adopted a negative opinion for three medicines in 2022. When the Committee cannot reach an agreement on a positive benefit-risk balance, it issues a negative opinion on the marketing authorisation application and elaborates on the grounds for this opinion. Applicants have the right to request a re-examination of the negative opinion within 15 days of receipt of the notification.

More information is available on our website.

- Hervelous
- Omblastys
- Tuznue

[7] Most paediatric extensions of indication are based on the results of clinical studies agreed in the medicine's paediatric investigation plan (PIP).

[8] For vaccines and treatments for COVID-19 and mpox, see pages 5, 7 and 8.

KEEPING PATIENTS SAFE

Monitoring in real-life – optimising safe and effective use

Once a medicine has been authorised, EMA and the EU Member States continuously monitor the quality, safety and the benefit-risk balance of the medicine used in clinical practice. This is to optimise how the medicine is used by patients to achieve its full benefit and to protect patients from avoidable side 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 2022 included:

Amfepramone obesity medicines	Recommendation to withdraw the marketing authorisations for **amfepramone obesity medicines** because risk management measures were not sufficiently effective to reduce the risk of serious side effects, such as pulmonary arterial hypertension (high blood pressure in the lung arteries) and dependency. In addition, there was evidence of use during pregnancy, which could pose risks to the unborn baby.
Dexmedetomidine	Update of the product information of **dexmedetomidine** to highlight the increased risk of mortality when administering dexmedetomidine in intensive care unit (ICU) patients aged 65 years and less, compared with alternative sedatives.
Hydroxyethyl-starch (HES) solutions	Recommendation to suspend marketing authorisations for **hydroxyethyl-starch (HES) solutions** for infusion across the European Union (EU) to avoid their use outside the recommendations previously included in the product information to minimise the risk of kidney injury and death in certain patients (those critically ill, with burn injuries or with sepsis).
Infliximab	Update of the product information of **infliximab** to include a recommendation to postpone the use of live vaccines in infants who are exposed to infliximab during pregnancy or via breastfeeding.
Janus-kinase (JAK) inhibitors	Recommendation to only use **Janus-kinase (JAK) inhibitors** for inflammatory disorders if no suitable treatment alternatives are available for people at increased risk of major cardiovascular problems, those who smoke/ have smoked and those at increased risk of cancer. In addition, caution is advised for use in patients with risk factors for blood clots in the lungs and in deep veins(venous thromboembolism, VTE). The use of a lower dose is recommended in patients with risk factors.

Mavenclad (cladribine)	Update of the product information of **Mavenclad (cladribine)** to include the risk of serious liver injury and to conduct liver function tests during treatment. In case a patient develops liver injury, treatment with Mavenclad should be interrupted or discontinued, as appropriate.
Medicines containing nomegestrol or chlormadinone	Recommendation to add new measures to use **medicines containing nomegestrol or chlormadinone** at the lowest effective dose and for the shortest duration possible, and only when other interventions are not appropriate, and not to use these medicines in patients who have, or have had, meningioma.
Pholcodine-containing medicines	Recommendation to withdraw marketing authorisations of **pholcodine-containing medicines** across the European Union given the serious risk of anaphylactic reactions (sudden, severe and life-threatening allergic reactions) to certain medicines called neuromuscular blocking agents (NMBAs) used in anaesthesia in patients who have been previously treated with pholcodine.
Rubraca (rucaparib)	Recommendation to not use **Rubraca (rucaparib)** as third-line treatment for cancers of the ovary, fallopian tubes or peritoneum with a BRCA mutation in patients whose cancer has come back after at least two platinum-based chemotherapies and who cannot have further platinum-based therapy.
Stelara (ustekimab)	Revised warning against the use of live vaccines in infants exposed to **Stelara (ustekimab)** in utero for six months following birth or until the infant's serum levels of ustekinumab are undetectable.
Stresam (etifoxine)	New recommendations to avoid or discontinue the use of **Stresam (etifoxine)** in patients with severe skin reactions or severe liver problems after taking etifoxine.
Terlipressin-containing medicines	Recommendation to update the product information for **terlipressin-containing medicines** with warnings to reduce the risk of respiratory failure and sepsis when using terlipressin to treat kidney problems in people with advanced liver disease.
Xalkori (crizotinib)	Update of the product information of **Xalkori (crizotinib)** to reflect the risk of ocular toxicity, severe visual loss and the need to monitor paediatric patients for vision disorders. In addition, a dose reduction of Xalkori should be considered in patients who develop Grade 2 ocular disorders and treatment should be permanently discontinued if Grade 3 and 4 ocular disorders occur, unless another cause is identified.

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.

The CHMP recommended the suspension of marketing authorisations for some 100 medicines which obtained approval on the basis of flawed bioequivalence studies conducted by the contract research organisation **Synchron Research Services**, located in Ahmedabad, India. For around 20 medicines included in this review, bioequivalence data from other sources are available and the medicines concerned are therefore allowed to remain on the EU market. To lift the suspension, companies relying on data from Synchron Research Services must provide alternative data demonstrating bioequivalence.

Nitrosamines

All marketing authorisation holders (MAHs) have continued to report on finished products at risk of N-nitrosamine presence in line with the requirements for the 'call for review' to MAHs. Competent authorities assessed notifications of products containing N-nitrosamines and, where necessary, took actions to protect patient safety whilst avoiding shortages of critical medicines. Some deadlines have been extended to allow companies more time to perform thorough investigations and establish required risk-mitigating actions in light of new scientific developments since 2020.

The Nitrosamine Implementation Oversight Group (NIOG) oversaw a harmonised implementation of the CHMP's Article 5(3) opinion on nitrosamines adopted in 2020. This involved engaging with industry to discuss challenges and solutions to the ongoing 'call for review' process and cooperating with other regulatory authorities to facilitate international alignment. Highlights of these interactions are available here.

The NIOG also issued guidance to facilitate compliance with the call for review, ensuring harmonisation of assessment and prioritisation, and approaches for temporary limits for nitrosamines to mitigate the risk of shortages of medicines while ensuring patient safety.

The EU Regulatory Network implemented measures to reduce potential risks associated with nitrosamines in medicines and ensure that regulators are better prepared to manage cases of unexpected impurities, as agreed in the implementation plan to address the lessons learnt on the presence of nitrosamines in sartan medicines.

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