



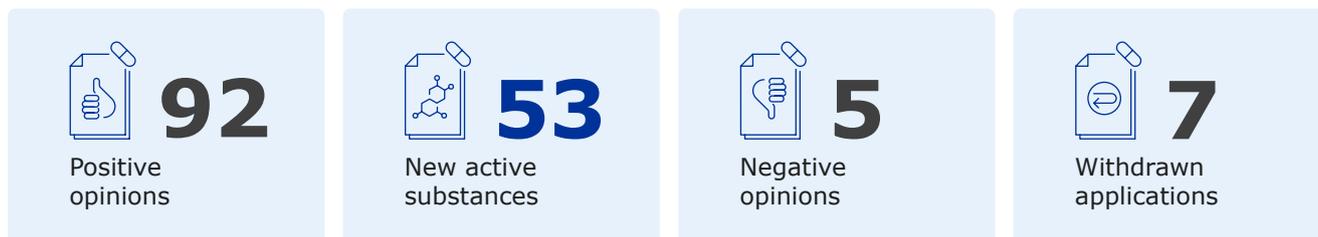
EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Human Medicines Highlights 2021



## AUTHORISATION OF NEW MEDICINES

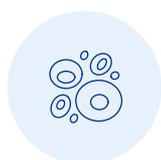
Key figures on the European Medicines Agency's (EMA) recommendations for the authorisation of new medicines in 2021:



*See more on the new recommendations from page 3.*

## KEEPING PATIENTS SAFE

Once a medicine has been put on the market, EMA and the European Union Member States continuously monitor its quality and benefit/risk balance. Important new safety advice issued in 2021 included:



Recommendation to update the existing warning on ifosfamide-induced encephalopathy with further details on its characteristics and risk factors, as well as highlighting the need to closely monitor patients receiving **ifosfamide solutions**.



Recommendation to only use **Xeljanz** in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors when no suitable treatment alternative is available.



Recommendation to update the product information and EU reminder card of **infliximab** (Remicade and biosimilars) to include stricter recommendations on the administration of live vaccines to infants breastfed by mothers receiving infliximab due to infant exposure via breast feeding.

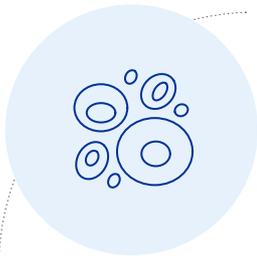
*See more on monitoring of medicines from page 12.*

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 their orphan designation confirmed by 31 December 2021. 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.

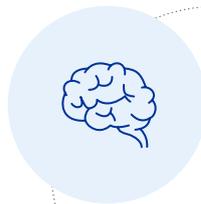
# MEDICINES RECOMMENDED FOR APPROVAL

## Cancer



**Abecma** ● ● ● ● ●  
 Abevmy ●  
 Abiraterone Accord  
 Abiraterone Krka  
 Abiraterone Mylan  
 Alymsys ●  
**Gavreto** ●  
 Imatinib Koanaa  
**Jemperli** ●  
 Lextemy\* ●  
**Lumykras** ●  
**Nexpvio** ●  
 Oyavas ●  
**Padcev**  
**Pemazyre** ● ●  
**Qinlock** ●  
**Rybrevant** ●  
**Tepmetko**  
**Trodelyv** ● ●  
**Voraxaze** ● ●

## Neurology



**Byfavo**  
**Evrysdi** ● ● ● ● ●  
 Fingolimod Mylan  
 Kesimpta  
**Koselugo** ● ● ●  
 Ontilyv  
 Ontozry  
 Ozawade  
 Ponvory  
**Skysona\*** ● ● ● ● ●  
 Sugammadex Mylan  
 Vumerity  
**Vyepti**

## Immunology/ Rheumatology/ Transplantation



Hukyndra ●  
 Icatibant Accord  
 Jayempi  
 Libmyris ●  
 Orladeyo  
**Saphnelo**  
**Tavneos** ●  
**Voxzogo** ●

## Covid-19



**COVID-19 Vaccine Janssen** ●  
**Nuvaxovid** ●  
**Regkirona**  
**Ronapreve**  
**Spikevax** ●  
**Vaxzevria** ●  
**Xevudy**

## Endocrinology



Efmody  
**Lonapegsomatropin Ascendis Pharma** ●  
**Ngenla** ●  
 Sitagliptin SUN  
 Sitagliptin/Metformin hydrochloride Mylan  
**Sogroya** ●  
 Wegovy  
**Yselyt**

## Cardiovascular



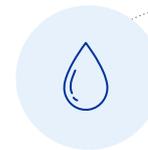
**Kerendia**  
 Rivaroxaban Mylan  
**Vazkepa**  
**Verquvo**

## Dermatology



Adtralza  
**Bimzelx**  
**Cibinqo**  
**Klisyri**

## Haematology/ Haemostaseology



Aspaveli ●  
**Brukinsa**  
**Copiktra**  
**Evrenzo**  
**Minjuvi** ● ●  
 Onureg  
**Oxbryta** ● ●  
 Thiotepa Riemser

## Metabolism



**Evkeeza** ●  
**Incivree** ● ● ●  
 Nexviadyme  
 Sapropterin Dipharma

## Ophthalmology



Byooviz ●  
**Enspryng** ●  
**Uplizna**

## Pneumology/ Allergology



BroPair Spiromax  
 Riltrava Aerosphere  
 Seffalair Spiromax

## Reproductive



**Drovelis**  
**Lydisilka**  
**Ryeqo**

## Infections



**Artesunate Amivas** ●  
**Tecovirimat SIGA** ●

## Vaccines



**Apexxnar**  
**Vaxneuvance**

## Gastroenterology/ Hepatology



Bylvay ● ● ● ● ●

## Diagnostic agents



Celsunax

## Psychiatry



Okedi

● 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**

\* The marketing authorisation has been withdrawn at the request of the marketing authorisation holder.

## OUTSTANDING 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 2021 that represent significant progress in their therapeutic areas\*:



### Cancer

#### Abecma

the first cell-based gene therapy to treat adults with relapsed and refractory multiple myeloma who have received at least three previous therapies and whose cancer has worsened since receiving the last treatment.

#### Trodelyv

a first-in-class medicine to treat adults with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for advanced disease.



### Gastroenterology/ Hepatology

#### Bylvay

the first treatment for progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.



### Immunology/ Rheumatology/ Transplantation

#### Tavneos

a first-in-class medicine to treat adults with severe, active granulomatosis with polyangiitis or microscopic polyangiitis, a rare type of inflammation of the blood vessels.

#### Voxzogo

to treat achondroplasia, a condition that impairs bone growth and causes dwarfism, in patients two years of age and above whose epiphyses are not closed.



### Metabolism

#### Incivree

for the treatment of obesity and the control of hunger associated with genetic deficiencies of the melanocortin 4 receptor (MC4R) pathway.



### Neurology

#### Evrysdi

the first oral treatment for patients with certain types of spinal muscular atrophy, a rare and often fatal genetic disease that causes muscle weakness and progressive loss of movement.



### Ophthalmology

#### Enspryng

a treatment for neuromyelitis optica spectrum disorders (NMOSD) in patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.

\* Medicines and vaccines to treat COVID-19 are listed in the 'Highlights on COVID-19' section.

## Highlights on COVID-19

EMA is contributing to tackling the COVID-19 pandemic 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.



### Vaccines

#### Vaccines approved to prevent coronavirus disease (COVID-19)

In people from 18 years of age:

- **January**
  - Spikevax** (Moderna)
  - Vaxzevria** (AstraZeneca)
- **March**
  - COVID-19 Vaccine Janssen**
- **December**
  - Nuvaxovid** (Novavax)



In children and adolescents:

- **May**
  - Comirnaty** in 12 to 15-year-olds
- **July**
  - Spikevax** in 12 to 17-year-olds
- **November**
  - Comirnaty** in 5 to 11-year-olds

The use of Spikevax in children aged 6 to 11 is under evaluation.

Boosters and extra doses in people from 18 years of age:

- **October**
  - Spikevax and Comirnaty**, booster at least 6 months after second dose and extra dose for severely immunocompromised people at least 28 days after second dose.
- **December**
  - COVID-19 Vaccine Janssen**, booster at least two months after first dose and heterologous booster at least six months after full vaccination with Comirnaty or Spikevax.

The conditional marketing authorisations for Spikevax, Comirnaty and Vaxzevria were renewed in 2021. EMA recommended the renewal of the conditional marketing authorisation for COVID-19 Vaccine Janssen in December.

## Adaptation of vaccines

In February, EMA issued guidance outlining the data requirements (clinical, non-clinical and quality) for companies planning to modify their vaccines in order to address coronavirus variants.

## Manufacturing

One of the major challenges with new vaccines is ensuring adequate supply and a reliable manufacturing process. Throughout 2021, EMA approved **new manufacturing sites and lines**, additional suppliers of raw materials and other manufacturing changes to enable a rapid scale-up of the production of Comirnaty, Spikevax, Vaxzevria and COVID-19 Vaccine Janssen. The number of approved manufacturing sites rose from 19 to 52, leading to a huge increase in vaccine supply.

## Safety updates

**Below is a high-level summary of important safety updates in 2021. For details on the safety information of each vaccine, please see [Safety of COVID-19 vaccines](#).**

EMA's safety committee (PRAC) issued monthly safety updates on every authorised COVID-19 vaccine reflecting data collected and assessed since the vaccine's authorisation.

In April, EMA concluded that blood clots with low blood platelets (thrombosis with thrombocytopenia syndrome or TTS) should be listed as very rare side effect of Vaxzevria. Subsequently, further analyses put the risk of TTS in the context of the vaccine's benefits for different age groups and different rates of infection to inform national decisions on the roll out of the vaccine.

The PRAC also concluded that TTS should be added as a very rare side effect for COVID-19 Vaccine Janssen, acting before the vaccine was even rolled out in the EU.

In June, EMA recommended that people with a medical history of capillary leak syndrome (CLS) must not be vaccinated with Vaxzevria, and that CLS should be included as a very rare side effect in the product information.

In July, EMA recommended listing Guillain-Barré syndrome as a very rare side effect of COVID-19 Vaccine Janssen and listing myocarditis and pericarditis as new side effects in the product information of Comirnaty and Spikevax. EMA also recommended that people with a medical history

of CLS must not be vaccinated with COVID-19 Vaccine Janssen, and that CLS should be included as a very rare side effect in the product information.

In August, the PRAC recommended to include immune thrombocytopenia as an adverse reaction for COVID-19 Vaccine Janssen.

In September, the PRAC recommended listing Guillain-Barré syndrome as a very rare side effect of Vaxzevria.

In October, the PRAC recommended listing venous thromboembolism (VTE) as a very rare side effect of COVID-19 Vaccine Janssen in the product information, to raise awareness especially in people with an increased risk of VTE. In addition, transverse myelitis was also listed as a side effect. PRAC also recommended listing immune thrombocytopenia as a side effect in the product information of Vaxzevria.

In December, the PRAC assessed data on the known risk of myocarditis and pericarditis following vaccination with Comirnaty and Spikevax, including evidence from two large European epidemiological studies, and concluded that the risk for both of these conditions is overall very rare.

## Vaccines under review

As of end of December 2021, four vaccines were under rolling review (COVID-19 Vaccine (Vero Cell) Inactivated, Sputnik V Gam-COVID-Vac, Vidprevtyn and VLA2001).





## Therapeutics

### Therapeutics approved

#### November

First monoclonal antibodies to treat COVID-19:

**Ronapreve**, to treat COVID-19 in patients from 12 years of age and weighing at least 40 kilograms who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. It can also be used for preventing COVID-19.

**Regkirona**, to treat adults with COVID-19 who do not require supplemental oxygen and who are also at increased risk of their disease becoming severe.

#### December

**Xevudy**, third monoclonal antibody to treat COVID-19 in patients from 12 years of age and weighing at least 40 kilograms who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.

**RoActemra**, extension of indication to include treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation.

**Kineret**, extension of indication to include treatment of COVID-19 in adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) and who are at risk of progressing to severe respiratory failure (determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR)  $\geq$  6ng/).

**Veklury**, extension of indication to include treatment of adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

The conditional marketing authorisation for Veklury has been renewed.



### Safety updates

In June EMA recommended a change to the product information for Veklury listing sinus bradycardia (heart beats more slowly than usual) as an adverse reaction of unknown frequency.

### Therapeutics under review

As of end of December 2021, an oral antiviral, Lagevrio (molnupiravir), and an existing immunosuppressant medicine, Olumiant (baricitinib), were under evaluation. Another oral antiviral, Paxlovid (PF-07321332/ritonavir), and a combination of monoclonal antibodies, Evusheld (tixagevimab/cilgavimab), were under rolling review.

### Use of medicines not authorised to treat COVID-19\*

EMA adopted harmonised scientific opinions on six treatments which at the time were not authorised to treat COVID-19: two combinations of monoclonal antibodies, Ronapreve (casirivimab/imdevimab) and bamlanivimab/etesevimab, two single antibodies, Regkirona (regdanvimab) and Xevudy (sotrovimab), and two antivirals, Lagevrio (molnupiravir) and Paxlovid (PF-07321332/ritonavir). This advice supports national authorities who may decide on possible early use of the medicine prior to marketing authorisation.

In March 2021, EMA concluded that existing published data on ivermectin from laboratory and observational studies, clinical trials and meta-analyses, do not support its use to prevent or treat COVID-19 outside controlled clinical trials.

In May 2021, EMA advised healthcare professionals that there is currently insufficient evidence that inhaled corticosteroids are beneficial for people with COVID-19.

\* Ronapreve, Regkirona, Xevudy and Paxlovid have since been authorised to treat COVID-19.

# EARLY ACCESS TO MEDICINES THAT ADDRESS PUBLIC HEALTH NEEDS

## Accelerated assessments

Three\* 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

#### Trodelvy

to treat adults with unresectable or metastatic triple-negative breast cancer.



### Neurology

#### Evrysdi

to treat patients with certain types of spinal muscular atrophy.



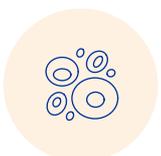
### Gastroenterology/ Hepatology

#### Bylvay

for the treatment of progressive familial intrahepatic cholestasis in patients aged 6 months or older.

## Conditional marketing authorisations

Thirteen 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 obligations to generate complete data on the medicines after the authorisation.



### Cancer

#### Abecma

to treat adults with relapsed and refractory multiple myeloma who have received at least three previous therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and whose cancer has worsened since receiving the last treatment.

### Gavreto

for the treatment of non-small cell lung cancer.

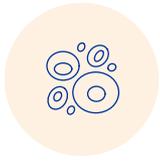
### Jemperli

for the treatment of certain types of recurrent or advanced endometrial cancer.

### Lumykras

for treating non-small cell lung cancer in patients with a specific mutation, G12C, in the KRAS protein.

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



## Cancer

### Nexpovio

for the treatment of relapsed and refractory multiple myeloma.

### Pemazyre

for the second-line treatment of advanced or metastatic cholangiocarcinoma (bile duct cancer).

### Rybrevant

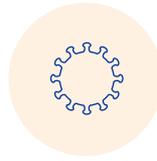
for the treatment of non-small cell lung cancer.



## Neurology

### Koselugo

for the treatment of paediatric patients with neurofibromatosis type 1 (NF1) plexiform neurofibromas.



## COVID-19

### COVID-19 Vaccine Janssen

a vaccine to prevent COVID-19 in people aged 18 years and older.

### Nuvaxovid

a vaccine to prevent COVID-19 in people from 18 years of age.

### Spikevax

a vaccine to prevent COVID-19 in people aged 12 years and older.

### Vaxzevria

a vaccine to prevent COVID-19 in people aged 18 years and older.



## Haematology/ Haemostaseology

### Minjuvi

to treat adults with relapsed or refractory diffuse large B-cell lymphoma who are not eligible for autologous stem-cell transplant.

---

## Approval under exceptional circumstances

Four 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

### Voraxaze

to reduce toxic plasma methotrexate concentration in adults and children with delayed methotrexate elimination or at risk of methotrexate toxicity.



## Infections

### Tecovirimat SIGA

to treat orthopoxvirus disease (smallpox, monkeypox, cowpox, and vaccinia complications).



## Gastroenterology/ Hepatology

### Bylvay

for the treatment of progressive familial intrahepatic cholestasis in patients aged 6 months or older.



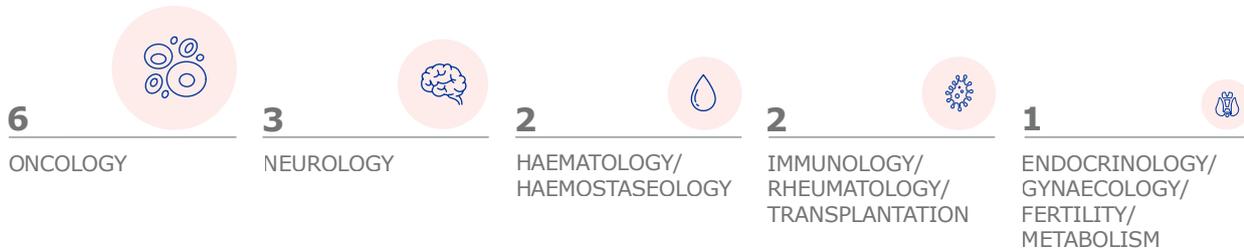
## Metabolism

### Evkeeza

to treat patients aged 12 years and older with homozygous familial hypercholesterolemia.

## 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, six medicines with PRIME designation were recommended for approval (Abecma, Bylvay, Evrysdi, Imcivree, Oxbryta and Skysona). 14 medicines under development were included in the scheme in 2021 in five medical specialties:

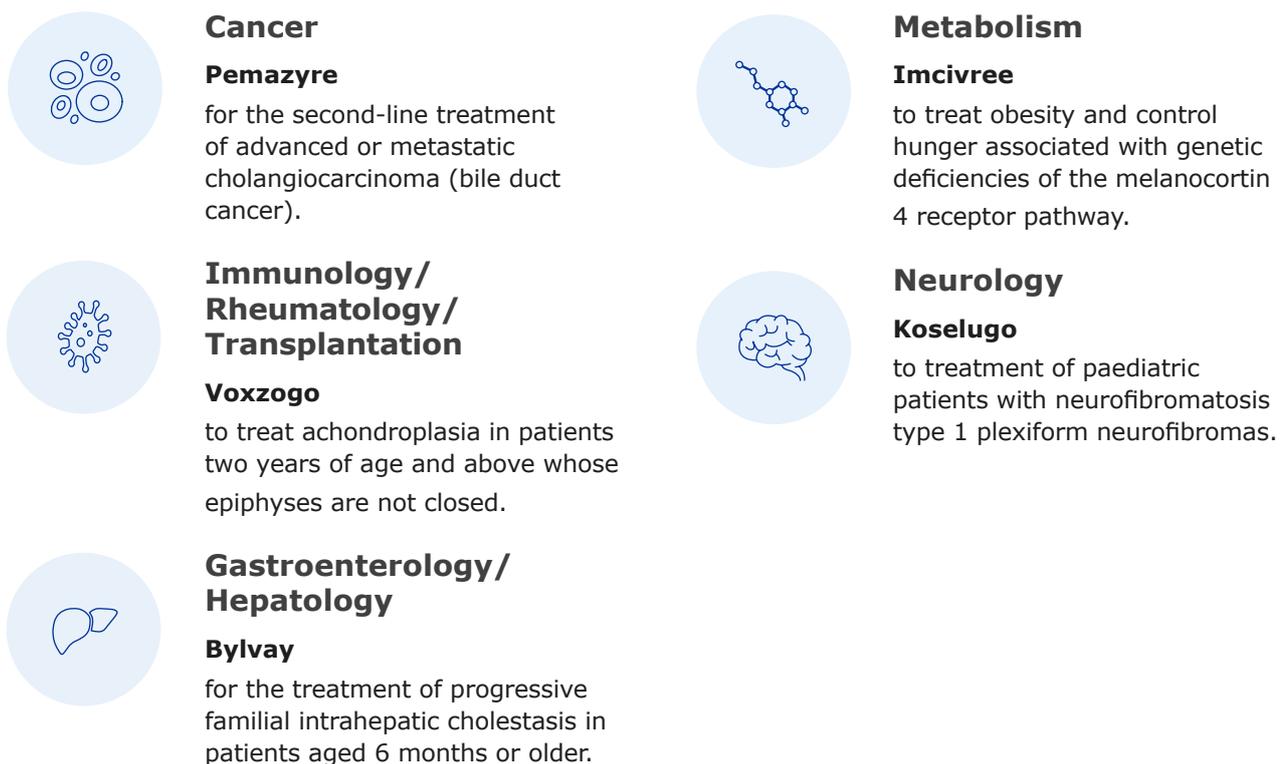


## MEDICINES FOR RARE DISEASES

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 2021, 19 medicines had 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:



## NEW USES FOR EXISTING MEDICINES

89 extensions of indication were recommended in 2021, including 35 for paediatric use. 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:



### Cardiovascular

#### Volibris

for the treatment of pulmonary arterial hypertension (PAH) in adolescents and children (aged 8 to less than 18 years).

### Endocrinology

#### Forxiga

for the treatment of type 2 diabetes in children from 10 years of age whose condition is not controlled well enough.

#### Saxenda

as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years with obesity and body weight above 60 kg.



### Immunology/ Rheumatology/ Transplantation

#### Benlysta

the first centrally approved medicine for the treatment of active lupus nephritis.

### Pneumology/Allergology

#### Nucala

as an add-on treatment for relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis in patients aged 6 years and older.



## NEGATIVE OPINIONS

The Committee for Medical Products for Human Use (CHMP) adopted a negative opinion for five medicines in 2021.

- Aduhelm
- Flynpovi
- Ipique
- Nouryant
- Raylumis

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](#).

\* Treatments for COVID-19 are included in the 'Highlights on COVID-19' section.

## 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 2021 included:

#### **Alkindi**

Recommended actions to minimise the risk of acute adrenal insufficiency in children that may occur when switching from conventional oral hydrocortisone formulations to **Alkindi** granules, due to potential inaccurate dosing with other oral hydrocortisone formulations.

#### **Ifosfamide solutions**

Update of the product information to provide further details on the characteristics and risk factors of ifosfamide-induced encephalopathy, as well as highlighting the need to closely monitor patients receiving **ifosfamide solutions**.

#### **Immune checkpoint inhibitors** (Tecentriq, Bavencio, Libtayo, Imfinzi, Yervoy, Keytruda, Opdivo)

Update of the product information of **immune checkpoint inhibitors** to include a class effect of immune-mediated non-infectious cystitis.

#### **Infliximab** (Remicade and biosimilars)

Update the product information and EU reminder card of **infliximab** (Remicade and biosimilars) to include stricter recommendations on the administration of live vaccines to infants breastfed by mothers receiving infliximab due to infant exposure via breast feeding.

#### **Invanz**

Update of the product information of **Invanz** to consider discontinuation of treatment if Invanz-induced encephalopathy is suspected (e.g. myoclonus, seizures, altered mental status, depressed level of consciousness). Patients with renal impairment are at higher risk of Invanz-induced encephalopathy and the resolution may be prolonged.

#### **Kadcyla**

Update of product information of **Kadcyla** to include new recommendations and measures to closely monitor the infusion site for possible subcutaneous infiltration during drug administration, as cases of delayed epidermal injury or necrosis following extravasation (when a medicine that is normally injected into a vein leaks or is accidentally injected into the tissue surrounding the vein, where it can cause serious damage) have been observed.

### **Kineret, Ilaris**

Update of the product information of **Kineret and Ilaris** with recommendations and warnings on adverse drug reactions with eosinophilia and systemic symptoms (DRESS) predominantly in patients with systemic juvenile idiopathic arthritis (sJIA).

### **Venclyxto**

Update of the product information of **Venclyxto** to include new recommendations and measures for the mitigation of the risk of tumour lysis syndrome (a serious complication with rapid break down of cancer cells).

### **Xeljanz**

New recommendation to only use **Xeljanz** in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors when no suitable treatment alternative is available.

## **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.



### **Nitrosamines**

The identification by marketing authorisation holders of active substances and finished products at risk of N-nitrosamine formation or (cross-) contamination was completed. All human chemical and biological products for which a theoretical potential risk of nitrosamine contamination was identified are undergoing confirmatory testing. This applies to 16% of chemical and 1% of biological centrally authorised products. Results are expected by September 2022 and July 2023, respectively. In March 2021, the European medicines regulatory network established the Nitrosamine Implementation Oversight Group (NIOG) to oversee the implementation of the CHMP's Article 5(3) opinion on nitrosamines in human medicines.

A system was put in place to ensure patient safety whilst avoiding shortages of critical medicines. A Multidisciplinary Expert Group (NMEG) proposed interim safe limits for a limited duration of time whilst MAHs implement their corrective and preventive actions. This system has facilitated the successful management of nitrosamine levels in **metformin and rifampicin**.

Official medicines control laboratories (OMCLs) have tested products containing these active substances in order to independently evaluate the quality of distributed medicines.

EMA's CHMP concluded a review of the presence of N nitroso-varenicline, a nitrosamine impurity, in **Champix** (varenicline), a smoking cessation medicine. The marketing authorisation holder has to fulfill certain quality requirements to ensure that Champix conforms to acceptable nitrosamine intake limits for EU medicines, calculated in line with the ICH M7 guideline. As a precaution, the marketing authorisation holder recalled several batches and paused distribution of Champix, as of June 2021.

**European Medicines Agency**

Domenico Scarlattilaan 6  
1083 HS Amsterdam  
The Netherlands

**Telephone** +31 (0)88 781 6000

**Send a question:** [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact)

**[www.ema.europa.eu](http://www.ema.europa.eu)**

**Human Medicines Highlights 2021**