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Oncology Captures One In Three New EU Drug Approvals In 2016

by Ian Schofield

2016 saw 30 new active substances approved in the EU, in a total of 29 different products, of which 10 were for cancer indications. Also approved were a range of combinations of old and new drugs, some new uses, and a number of biosimilars and generics. 14 of the products approved during the year were for rare diseases, while eight received a conditional marketing authorization.

Drugs for use in oncology increased their share of EU initial marketing authorizations in 2016, accounting for a third of the 30 new active substances approved by the European Commission in the year to Dec. 22.

Although the total number of new active substances (NASs) in 2016 was significantly down on the high of 46 seen in the previous year, it was pretty much in line with the 34 NASs approved in 2014. Among the approvals were a number of combination treatments, including one containing two new active substances – *Merck Sharp & Dohme Ltd.*'s hepatitis C treatment Zepatier (elbasvir plus grazoprevir).

The commission also gave the green light to a number of new combinations of existing medicines, a smattering of biosimilars and generics, and some new uses (and names) for old drugs.

The types of products and their routes to approval illustrate the growing complexity of new drugs for less common conditions and for those with unmet needs. Fourteen products approved in 2016 (not all of them NASs) were orphan drugs, while the number of products given a conditional marketing authorization – where approval is granted on condition that more data are produced to support a switch to a full marketing authorization – doubled to eight. Six of these were for oncology drugs.

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Oncology

The oncology area saw 10 new active substance approvals in 2016, including *Pfizer Inc.*'s *Ibrance* (palbociclib) for HR-positive, HER2-negative locally advanced or metastatic breast cancer – the first cyclin-dependent kinase 4/6 inhibitor to be given the green light in Europe. The HR+/HER2- breast cancer market is valued at around $3.4bn in the US, Japan and the five major EU markets, a figure that Datamonitor Healthcare forecasts could rise to $10.7bn by 2022, largely due to the uptake of Ibrance and the approval of other late-phase pipeline candidates.

Four of the new cancer drugs that were given a conditional marketing authorization also had orphan status:

- *Eli Lilly & Co.*'s *Lartruvo* (olaratumab), for soft tissue sarcoma in adults non-responsive to radiotherapy or surgery. Lartruvo also benefited from an accelerated assessment by the European Medicines Agency's scientific committee, the CHMP. This was Lilly's first conditional approval in the EU: it has been asked to produce post-authorization data from the ongoing Phase III ANNOUNCE study, which is expected to complete in 2019.
- *AbbVie Inc./Roche*'s *Venclyxto* (venetoclax) for adults with chronic lymphocytic leukemia. This is a first-in-class BCL2-specific oral inhibitor, and, according to the companies, the first medicine approved that is designed to trigger a natural process that helps cells self-destruct in CLL patients who have received previous treatment or who have a high-risk form of the disease.
- *Takeda Pharmaceutical Co. Ltd.*'s *Ninlaro* (ixazomib) for multiple myeloma in patients who have taken at least one prior therapy. This was approved only after the CHMP reversed an initial negative opinion on the product and on condition that the company provide more confirmatory data on its effectiveness.
- *MolMed SPA*'s *Zalmoxis*, consisting of genetically modified allogeneic T cells, for adjunctive treatment in haploidentical hematopoietic cell transplantation in adults with high-risk hematological malignancies.

Key EU Approval Data For 2016

30 new active substances, in a total of 29 different products

10 new oncology treatments

9 new combinations

14 orphans

8 conditional marketing authorizations

4 biosimilars

A handful of generics

Top NAS categories: oncology, alimentary/metabolic, neurology

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Two new drugs were approved for multiple myeloma. *Janssen-Cilag GMBH*'s orphandrug *Darzalex* (daratumumab), a first-in-class anti-CD38 antibody intended for relapsed and refractory multiple myeloma, received a CMA.

The approval of Darzalex came hot on the heels of that of *Bristol-Myers Squibb Co.*'s *Empliciti* (elotuzumab), which underwent accelerated assessment for use in combination with lenalidomide (*Celgene Corp.*'s *Revlimid*) and dexamethasone in adult multiple myeloma patients who have received at least one prior therapy. Emplicit will be entering an increasingly crowded market, but its approval for second-line or higher use should help it stand out from the crowd. It is expected to have the edge over Darzalex, as it is approved for use earlier in the treatment paradigm, although Darzalex is expected to move to earlier-stage use in due course.

One other new oncology drug was given a conditional approval: *AstraZeneca PLC*'s *Tagrisso* (osimertinib) for locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (following accelerated assessment). As a condition of the approval, the company must provide data from the Phase III AURA3 study comparing osimertinib with platinum-based chemotherapy, which is expected to be available in June 2017.

Two other cancer products received EU approval. *Servier SA*'s *Lonsurf* (trifluridine/tipiracil) was OKd for metastatic colorectal cancer (tipiracil is the new active substance in the combination). Although it is authorized only for third- and fourth-line settings, these are still areas with high unmet needs.

Lilly's *Portrazza* (necitumumab) was OKd for locally advanced or metastatic EGFR-expressing squamous non-small-cell lung cancer in chemotherapy-naïve patients.

Alimentary/Metabolic

Four new products were approved in the alimentary/metabolic disease area, including *Grunenthal GMBH*'s *Zurampic* (lesinurad) for hyperuricemia in gout patients. The drug was developed by AstraZeneca, which licensed the European and Latin American rights to the German company earlier this year. It is also one of the first products for which the EMA has published clinical reports under its proactive clinical data publication policy. (Also see "*It's Started: EMA Proactively Publishes Clinical Data On New Drugs*" - Pink Sheet, 21 Oct, 2016.)

Amgen Inc.'s *Parsabiv* (etelcalcetide) was authorized for secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy. While the drug, a follow-on from *Mimpara* (cinacalcet), seems to have passed through the CHMP process without much ado, it has been held up in the US, where FDA issued a complete response letter in August. (Also see "*Amgen's Parsabiv's EU Approval Contrasts With US FDA Rejection*" - Pink Sheet, 16 Nov, 2016.)

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Representing only the second treatment for primary biliary cholangitis was *Intercept Pharmaceuticals Inc.*'s orphan drug *Ocaliva* (obeticholic acid), which is indicated for use with the only other available treatment for the condition, ursodeoxycholic acid (UDCA). The product, a farnesoid X receptor agonist, was given a conditional marketing authorization; Intercept will need to provide further data from the COBALT outcomes trial and a short-term study in patients with hepatic impairment.

The fourth approval in this area was Amicus Therapeutics' orphan drug *Galafold* (migalastat) for Fabry disease.

Neurology

Three new products were authorized in the neurology area in 2016. *Bioprojet*'s *Wakix* (pitolisant HCl) is a first-in-class orphan drug that acts on histamine H3 receptors in the brain and is intended to treat narcolepsy with or without cataplexy, while Bial's *Ongentys* (opicapone) is for adjunctive therapy in adults with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DOPA decarboxylase inhibitors (DDCIs). The third drug approved was *UCB Pharma SA*'s epilepsy treatment *Briviact* (brivaracetam).

Infectious Diseases

In the infectious diseases category, two new combination drugs were approved for hepatitis C. One was MS&D's *Zepatier*, a fixed-dose combination of two NAS, elbasvir and grazoprevir. Approved in July, it was due to launch across Europe starting in late November. The other was *Epclusa* (sofosbuvir/velpatasvir) from *Gilead Sciences Inc.* (velpatasvir is the NAS).

Epclusa will probably be the more successful of the two combinations "because it is the first pan-genotypic regimen to be approved and will be positioned as a one-size-fits-all once daily cure," according to Michael Haydock, lead analyst at Datamonitor Healthcare.

Illustrating the dearth of research in the antibacterial area, only one new NAS-containing product, AstraZeneca's *Zavicefta* (a combination of ceftazidime and the new beta-lactamase inhibitor avibactam), was approved in 2016. It is indicated for adults with multi-drug resistant bacteria and other severe bacterial infections, including carbapenem-resistant *Enterobacteriaceae*.

One new vaccine was approved in 2016: *MedImmune LLC*'s pandemic H5N1 flu vaccine, for prophylactic use in an officially declared pandemic situation in people aged 12 months to 18 years. This was a conditional approval.

Other New Substances

Two hemophilia B products were approved, both of them with orphan designation: *CSL Behring*'s

Idelvion (albutrepenonacog alfa) and *Swedish Orphan Biovitrum AB*'s *Alprolix* (eftrenonacog alfa). A European Commission decision transferring the marketing authorization for Alprolix to Swedish Orphan from *Biogen Inc.* was published in September.

GlaxoSmithKline PLC saw its orphan drug *Strimvelis* (autologous CD34+ enriched cell fraction) approved for severe combined immunodeficiency due to adenosine deaminase deficiency (ADA) deficiency. The company has completed significant studies contained in the pediatric investigation plan (PIP) for the product, and so its market exclusivity has been extended from 10 to 12 years, in accordance with the legislation.

The CHMP said that the benefits of *Actelion Pharmaceuticals Ltd.*'s *Uptravi* (selexipag) for pulmonary arterial hypertension included dilation of the pulmonary arteries as well as antiprofilerative and antifibrotic effects, which decrease pulmonary arterial pressure and delay disease progression.

Lilly's *Taltz* (ixekizumab) is a new treatment for moderate to severe plaque psoriasis in adults that binds with high affinity and specificity to both forms of interleukin 17A. The CHMP described Taltz's benefits as being its significant and clinically relevant effects compared with placebo or etanercept.

Teva Pharmaceutical Industries Ltd.'s *Cinqaero* (reslizumab) is an add-on therapy in severe eosinophilic asthma in adults whose condition is inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

In a new departure in the wound healing department, Birken AG saw its birch bark extract, *Episalvan*, authorized for the treatment of partial thickness wounds in adults – this is the first treatment to receive EU centralized approval for this condition. Earlier this year, Birken was acquired by the UK specialty company *Amryt Pharma PLC*, which said it plans to develop Episalvan for epidermolysis bullosa in Europe and the US.

Allergan PLC Pharmaceuticals received approval for *Truberzi* (eluxadoline) for irritable bowel syndrome with diarrhea. The marketing authorization was granted in September 2016 to *Aptalis Pharmatech Inc.* but was transferred to Allergan in December.

Combinations Of Known Substances

A range of other products and combinations were approved in the EU in 2016. New combinations of existing drugs included:

- *Boehringer Ingelheim GMBH*'s *Glyxambi* (empagliflozin + linagliptin) for type 2 diabetes.
- Gilead's *Descovy*, a fixed-dose combination of emtricitabine and tenofovir alafenamide for

HIV. The company says Descovy has high antiviral activity at a dose of less than one-tenth of its marketed HIV therapy Viread (tenofovir disoproxil fumarate).

- Gilead's *Odefsey* (emtricitabine/tenofovir alafenamide/rilpivirine) for HIV infection resistant to NNRTIs, tenofovir or emtricitabine. This is a new once-daily single-tablet regimen.
- *Qtern* (saxagliptin/dapagliflozin), a new fixed-dose combination from AstraZeneca for type 2 diabetes in adults over 18.
- *Novartis AG*'s *Neparvis* (sacubitril/valsartan) twice-daily tablet for symptomatic chronic heart failure.

Some older products were approved for new uses and with new names. *Ipsen Bioscience Inc.*'s cabozantinib was approved as *Cabometyx*, an orphan drug for advanced renal cell carcinoma. This is a new indication for cabozantinib, which is already marketed as *Cometriq* for thyroid cancer. The commission said it offered "significant clinical benefit over existing therapies."

Eisai Europe Ltd. gained approval of lenvatinib as *Kisplyx* for the new indication of advanced renal cell carcinoma. It is currently authorised in the EU as *Lenvima* for thyroid cancer, while Biogen Idec's daclizumab was approved as *Zinbryta* for relapsing multiple sclerosis. Daclizumab used to be marketed as *Zenapax* for rejection in kidney transplants, but it was withdrawn in 2009 due to lack of demand.

Other treatments authorized in 2016 included:

- Sialanar (glycopyrronium bromide) from Proveca for chronic pathological drooling in children and adolescents with chronic neurological disorders, and
- Coagadex, Bio Products Laboratory's human coagulation factor X for hereditary factor X deficiency. This is an orphan drug, and is the only treatment specifically licensed for this disorder.
- *Bayer AG*/CSL Behring's Factor VIII product, Iblias/Kovaltry, a next-generation octocog alfa and a successor to Kogenate that the companies say benefits from a slightly longer half-life and better personalization of prophylactic use.
- *Ferring Pharmaceuticals AS*'s Rekovelle (follitropin delta), the first recombinant follicle stimulating hormone to be derived from a human cell line and the first to be administered with an individualized dosing regimen.
- Vaxelis, from *Sanofi Pasteur MSD*, a diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed) vaccine. It is a new-generation, fully-liquid, ready-to-use vaccine and the only hexavalent vaccine with five acellular pertussis antigens and Hib antigen conjugated to the outer membrane protein complex of Neisseria meningitidis.

- *Advanced Accelerator Applications SA*'s orphan drug, SomaKit TOC (edotreotide), for the diagnosis of gastro-entero-pancreatic neuroendocrine tumors.

Biosimilars And Generics

Of the four biosimilars approved for marketing in 2016, two were versions of *Sanofi*'s enoxaparin product *Clexane*: *PharmAthene Inc.*'s *Thorinane* and Techdow Europe's *Inhixa*. The other two were *Samsung Bioepis Co. Ltd.*'s *Flixabi* (infliximab/SB2, a version of J&J's Remicade) and *Benepali* (etanercept, Amgen's Enbrel).

Generic approvals in 2016 included emtricitabine/tenofovir, lopinavir/ritonavir, ivabradine, pemetrexed, bortezomib, palonosetron, zonisamide, and caspofungin.

New Active Substances Approved In The EU In 2016[1]

Product	Indication	Company
Alprolix (eftrenonacog alfa)	Hemophilia B	Swedish Orphan Biovitrum
Briviact (brivaracetam)	Epilepsy	UCB Pharma
Cinqaero (reslizumab)	Severe eosinophilic asthma	Teva Pharmaceuticals
Darzalex (daratumumab)	Multiple myeloma	Janssen-Cilag
Empliciti (elotuzumab)	Multiple myeloma	Bristol-Myers Squibb
Epclusa (sofosbuvir/velpatasvir*)	Hepatitis C	Gilead Sciences
Episalvan (birch bark extract)	Partial thickness wounds in adults	Birken AG[2]
Galafold (migalastat)	Fabry disease	Amicus Therapeutics
Ibrance (palbociclib)	HR-positive, HER2-negative locally advanced or metastatic breast cancer	Pfizer
Idelvion (albutrepenonacog alfa)	Hemophilia B	CSL Behring
Lartruvo (olaratumab)	Soft tissue sarcoma	Lilly
Lonsurf (trifluridine/tipiracil*)	Metastatic colorectal cancer	Servier
Ninlaro (ixazomib)	Multiple myeloma	Takeda Pharma
Ocaliva (obeticholic acid)	Primary biliary cholangitis	Intercept Pharma
Ongentys (opicapone)	Adjunctive therapy in Parkinson's	Bial
Pandemic H5N1 influenza vaccine	Flu prophylaxis	MedImmune
Parsabiv (etecalcetide)	SHPT in adults with chronic kidney disease	Amgen
Portrazza (necitumumab)	Non-small-cell lung cancer	Lilly
Strimvelis (autologous CD34+ cell fraction)	SCID due to ADA deficiency	GlaxoSmithKline
Tagrisso (osimertinib)	Non-small-cell lung cancer	AstraZeneca

Taltz (ixekizumab)	Plaque psoriasis	Lilly
Truberzi (eluxadoline)	Irritable bowel syndrome	Allergan
Uptravi (selexipag)	Pulmonary arterial hypertension	Actelion
Venclyxto (venetoclax)	Chronic lymphocytic leukemia	AbbVie/Roche
Wakix (pitolisant HCl)	Narcolepsy	Bioprojet Pharma
Zalmoxis (genetically modified T cells)	Hematopoietic cell transplantation in adults with high-risk hematological malignancies	MolMed
Zavicefta (ceftazidime/avibactam*)	Multi-drug resistant bacteria and other infections	AstraZeneca
Zepatier (elbasvir*/grazoprevir*)	Hepatitis C	Merck Sharp & Dohme
Zurampic (lesinurad)	Hyperuricemia in gout patients	Grünenthal

**Substance is a NAS.*

[1]The table and text of this article are based on information from the European Commission's database of new EU drug approvals as of Dec. 22, 2016, as well as other sources including the Pink Sheet, Scrip, and pharmaceutical companies.

[2]Birken was acquired by Amryt Pharma in 2016.