The work on the list of indispensable anti-cancer drugs was supported by the European Association of Hospital Pharmacists (EAHP)

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Working Group on unavailability in indispensable medicinal products JUNE 2021

List of indispensable anti-cancer drugs

The *Working Group on unavailability of indispensable medicinal products* of the French National Academy of Pharmacy has been at the origin of a report on the unavailability of essential medicines, published in June 2018[1]. It is continuing its work in the context of discussions, particularly at the European level, with a view towards both gradually restoring autonomy in the supply of health goods in Europe, and to seeking the most appropriate practical measures to reduce tension and supply disruptions.

For the Academy, the unavailability of medicines covers both the risks of shortages due to logistical or technical reasons for drug products on the market as well as shortages linked to the withdrawal of drugs from the market.

In its 2018 report, the Academy focused essentially on one major aspect of the unavailability of medicinal products: the unavailability of **old but indispensable medicinal products that are** still considered necessary[2] for therapy, despite the appearance of innovative medicines over the last twenty years, particularly those derived from biotechnology. In fact, most of the drugs that are used to treat patients today [as was seen during the Covid-19 health crisis] are **chemical molecules that** have long since fallen into the public domain (and were first marketed between the 1950s - sometimes even before - and the 1980s). This was recently the case for resuscitation drugs that were in short supply or under extreme stress during the health crisis.

This is also very much the case for cancer therapies and associated therapies.

[1] https://www.acadpharm.org/dos_public/2018_06_20_AnP_RAPPORT_INDISPONIBILITE_MED_VF1.pdf

[2] The academic report cites in particular "old" drugs for intensive care, oncology, infectious diseases, neurology, cardiology and paediatrics, which were first marketed between the 1950s and 1980s.

The companies that first marketed these molecules have either disappeared or merged into larger pharmaceutical groups, which have disengaged over time to focus on the development of therapeutic innovations, protected by a patent.

These "old" but still indispensable molecules are now largely marketed by specialized units of the pharmaceutical industry, known as **generic drugs,** some of which appeared *ex nihilo* in the 1990s and 2000s.

In terms of their availability on the market, **indispensable old anti-cancer medicinal products** are often victims of an economic reality linked to their age, which results in increasingly low prices that make them unprofitable for operators. However, these anticancer molecules require expensive operating conditions for their synthesis and processing into drugs. Indeed, these are molecules with high pharmacological and toxic activity (proven carcinogenic potential) requiring work in confinement with the implementation of expensive barrier technologies, sometimes even requiring totally dedicated and isolated factories and factory sectors. In addition to these constraints, there is another one, linked to the fact that most of the drugs are administered by injection, that of production in a sterile environment.

Thus, both the production of these active ingredients and the production of injectable forms are subject to quite costly technological constraints, which are understandable in terms of safety for handlers and the environment (protection against cytotoxic products) on the one hand, and patient safety (sterility) on the other. This explains why the number of chemical companies and pharmaceutical manufacturers is limited, or even insufficient, in the face of the growing worldwide demand.

Therefore, the Academy has been giving the alert for the last ten years or so about the need to rebuild **a market surveillance and investment strategy** in order to be less dependent on countries outside Europe, particularly in South-East Asia, which have been responsible for most of the world's chemical synthesis for the last twenty years.

The view of the Academy is that public authorities have a duty to protect citizens against possible shortages or interruption of availability (withdrawal from the market) for molecules that have fallen into the public domain.

The Academy is therefore in favour of the development of a European strategy to regain autonomy in the production of active ingredients that have fallen into the public domain and the medicines prepared from them. The COVID-19 health crisis has shown how much this regaining of autonomy is a geopolitical issue of the first order.

To assist in this process, the Academy wishes to draw up a list of active ingredients whose supply chain should be monitored, with the aim of restoring a sufficient level of production in Europe to cope with any crisis.

In this respect, the Academy notes with interest that the United States recently released the findings of an audit launched in February by President Joe BIDEN on four supply chains deemed key to **US sovereignty**, **including medicines**. To reverse the trend, the BIDEN administration will commission a public-private consortium to identify 50 to 100 products for which **domestic production** will be sought.

The Academy supports the possibility of the EU establishing a similar list. The Academy considers that the preservation and rebuilding of domestic production capacities in the EU for key products is essential to ensure the safety of European patients.

The Academy has worked first on resuscitation and cancer drugs and will continue its work on other therapeutic classes.

This report proposes **a reflection on the old anti-cancer drugs essential to the treatment of patients**. This work takes into account the reflections made in 2018 by a working group led by the National Cancer Institute, with which the Academy was associated and the result of which has not been made public. The molecules proposed for enhanced surveillance have all or almost all had breaks in supply in recent years.

This report is intended to contribute to the reflection on the consolidation of a European list of key products. The Academy draws attention to the fact that these lists will have to be regularly updated.

The creation of a European list of key products was supported by the European Association of Hospital Pharmacists (EAHP).

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1. OVERVIEW OF CANCER THERAPIES

Briefly, anti-cancer drugs can be divided into several major classes:

- conventional chemotherapy drugs, including cytotoxics;
- Targeted therapies, including monoclonal antibodies (including anti-angiogenic drugs), tyrosine kinase inhibitors (TKIs) and selective m-TOR inhibitors;
- proteasome inhibitors[3];
- specific immunotherapy drugs (interferon (IFN) - interleukins (IL) ;
- hormone therapy drugs (cytostatics).

The principle of treatment is to stop the multiplication (cytostatic) or destroy (cytotoxic) the malignant cells while preserving the healthy cells.

However, these treatments are highly toxic for healthy cells, and none of the cytotoxic drugs are selective for cancer cells. Thus, for all these drugs, the therapeutic margin is narrow. Moreover, in a population of malignant cells, the cells are not all at the same stage of reproduction: this makes it necessary to combine several molecules. Drug combinations also make it possible to increase efficacy while keeping the toxic effects as low as possible.

The combination of cytotoxic drugs (in particular) is the basis of many anti-cancer protocols. The combination aims to obtain either an additive or a synergistic effect. It should also be noted that the major innovations in cancer therapy over the last twenty years have largely been the result of step-by-step research into better sequencing of treatments according to the type of cancer and better control of dosage. This has resulted in increasingly well-tested protocols, which have progressively improved prognosis and obtained results that cannot be compared with those of the past, with a comparable product portfolio.

In this context, if a single drug is missing from a proven protocol, the difficult balance between effectiveness against cancer cells and reduction of undesirable effects on healthy tissues is disrupted, compromising the patient's outcome. **This less favourable outcome** is necessarily at the heart of the concerns of health professionals, who make every effort daily to ensure that every patient, in all their diversity, is supported in this vital struggle, to the best of their knowledge and the state of the art.

It is therefore essential to look at the availability of these molecules and useful dosage forms.

[3] Proteasome inhibitors are growth factor inhibitor treatments used to help kill cancer cells, because when they block proteasomes, proteins build up within the cells and destroy them

It is easy to understand that it is difficult to prioritize anti-cancer drugs, because by their very nature, many are "irreplaceable":

- There are indeed molecules that are found in **all** or almost **all the protocols**; these must obviously be available **in necessary and sufficient quantities to satisfy the demand** of all the Member States of the Union, and the question of production capacity arises because world demand is increasing;
- at the other end of the chain, there are also molecules that will only be useful in **rare** or even rarer **cases** (sometimes comparable to orphan diseases in terms of prevalence) but which are essential for the resolution of certain cancers, particularly in paediatrics; for them, there is the question of the number of industrial operators likely to respond to these "small markets" and **it is not unusual to see operators withdraw**, because the intrinsic manufacturing cost (linked to the various regulatory and technological constraints) cannot be compensated for by the volume.

In the next few paragraphs, we will review the DCIs that seem to require particular protection.

It is important to be aware that the proposed list will need to be regularly reviewed, particularly to add molecules.

Since it is impossible to know whether the phenomenon observed with very old molecules will not be reproduced in the future for molecules currently "protected" by a patent, when they fall into the public domain.

In particular, biological molecules (derived from biotechnology) do not figure greatly in the current list, because their profitability is assured at present. They will need to be monitored as they gradually enter the public domain. Most of these molecules are not produced in Europe.

However, for them, the "entry ticket" to benefit from the production of biosimilar medicines **on the European continent** will necessarily be higher because of the sophisticated technologies that their production requires. If we wish to aim for a certain degree of European autonomy, we must create correct mechanisms to facilitate their production on this territory for the benefit of European patients.

The medicines highlighted in red in this report are considered ESSENTIAL key products by the National Academy of Pharmacy.

2. THE LIST OF ESSENTIAL OLD CANCER DRUGS TO MONITOR AT THE MOMENT

2.1. Cytotoxics

These are essentially chemically synthesized molecules.

Cytotoxics are classified into 4 main subclasses:

- drugs that cause DNA strand abnormalities: alkylating agents;
- drugs that induce DNA breaks - intercalators: topoisomerase I and II inhibitors;
- drugs that induce DNA synthesis: antimetabolites;
- drugs that interact with tubulin (a protein that self-assembles to form microtubules, a key protein in cell division): mitotic spindle poisons.

The table below shows the main cytotoxics used to date. Those that are considered **IRREPLACEABLE AND ESSENTIAL and whose supply must be secured** are indicated in red.

Alkylants	Anti-metabolites		Intercalants	Spindle poisons
Nitrogen mustard **CYCLOPHOSPHAMIDE** **IFOSPHAMIDE** **MELPHALAN** ESTRAMUSTIN **BENDAMUSTIN** **CHORAMBUCIL**	**Folic antagonists** **METHOTREXATE** RALTITREXED **PEMETREXED**		**Topoisomerase I inhibitors** **IRINOTECAN** **TOPOTECAN**	**Vinca alkaloids** **VINCRISTINE** **VINBLASTIN** **VINDESINE** VINORELBINE
Ethylenes-Imines **THIOTEPA** **MITOMYCIN C**	**Pyrimidine antagonists** **FLUOROURACILE** **CAPECITABIN** **GEMCITABIN** **CYTARABINE**		**Topoisomerase II inhibitor** **ETOPOSIDE**	**Taxanes** **DOCETAXEL** **PACLITAXEL**
Organoplatins **CISPLATIN** **CARBOPLATIN** **OXALIPLATIN**	**Purine antagonists** **MERCAPTOPURINE** CLOFARABIN		**Anthracyclines** **DOXORUBICIN** **EPIRUBICIN** **DAUNORUBICIN**	**Other** ERIBULINE

			IDARUBICIN	
Alkylo-sulfonates **BUSULFAN** **PIPOBROMAN**	**Purine analogues** **FLUDARABIN** **CLADRIBINE** PENTOSTATIN		**Anthracene-dione** **MITOXANTHRONE**	
NItroso-urea **CARMUSTINE (BICNU)** **LOMUSTINE (CCNU)**	**Other** **HYDROXYCARBAMIDE**		**Other** **BLEOMYCINE**	
Other **CHLORMETHINE** **DACARBAZINE** **PROCARBAZINE**				
Multiple mechanisms **AZACITIDINE**				

2.2. Monoclonal antibodies

Monoclonal antibodies (mAbs) are used in multidrug therapy in combination with cytotoxic drugs. They have a specific mechanism of action by binding to cell surface receptors and blocking the transmission of the cell division message to the nucleus.

Monoclonal antibodies, produced by biotechnology, have suffered less from supply tensions to date, because they are still, even as biosimilars[4], economically viable.

Not all monoclonal antibodies are in the public domain and many are still marketed by the companies of origin.

However, it will be important, as they fall into the public domain (which is already the case for some), to ensure a certain autonomy for the European Union (transfer and search for operators on European territory).

As a first step, the Academy considers that the following mAbs should be secured:

- **TRASTUZUMAB** in adjuvant breast cancer in patients identified as HER +++ ;
- **RITUXIMAB** in onco-haematology ;

[4] A biosimilar medicine is a medicine which, like any biological medicine, is produced from a cell or living organism or derived from them. Its efficacy and adverse effects are equivalent to those of its reference biological medicine. Its marketing authorisation meets strict regulatory requirements to demonstrate that its pharmaceutical quality, efficacy and adverse effects are clinically equivalent to those of the reference biologic. It is possible to change a biological medicinal product by another one appearing on the list of biosimilar medicinal products established by the ANSM, which defines interchangeability3. This change must be decided between the doctor and the patient. (Source; HAS https://www.has-sante.fr/jcms/c_2807411/fr/les-medicaments-biosimilaires)

- **NIVOLUMAB:** it is essential in many protocols and in many cancers (melanoma, lung).

When the Academy surveyed hospital pharmacists in Europe with the help of the EAHP (European Association of Hospital Pharmacists), the monoclonal antibodies cited as sensitive, in addition to the three previously mentioned, were **PEMBROLIZUMAB**, **DURVALUMAB AND BEVACIZUMAB**.

List of the main current mAbs

DCI	Indications in cancer[5]
ALEMTUZUMAB	chronic lymphocytic leukaemia
BEVACIZUMAB	Colorectal, breast, bronchial, kidney
CATUMAXOMAB	Neoplastic ascites
CETUXIMAB	Colorectal, head and neck
DURVALUMAB	Extended stage small cell lung cancer (ES-SCLC)
IPILIMUMAB	melanoma
NIVOLUMAB	Melanoma, lung
OFATUMUMAB	chronic lymphocytic leukaemia
PANITUMUMAB	colorectal
PEMBROLIZUMAB	Melanoma, non-small cell lung cancer, Hodgkin's lymphoma
RITUXIMAB	Lymphoma, chronic lymphocytic leukaemia
TRASTUZUMAB	Breast, stomach

[5] For many of these mAbs, the indications are constantly evolving; the main fields of indications are listed in this table, for example.

2.3. Hormone therapy

The aim of hormone therapy is to inhibit hormone-stimulated tumour growth. In fact, the effects of physiological hormones may be suppressed in several ways

- suppression of hypothalamic stimulin production (chemical castration);
- inhibition of the synthesis of the hormones involved in the endocrine glands;
- receptor blockage.

Hormone therapy is mainly used for breast and prostate cancer.

2.3.1. Prostate cancer

The aim of hormone therapy in this cancer is to suppress the action of androgens.

There are several possible ways:

- chemical castration (LH-RH analogues);
- inhibition of androgen synthesis ;
- anti-androgens ;
- oestrogens : (discontinued).

Treatment of first-line metastatic disease is usually a combination of castration with an anti-androgen.

LH-RH agonist	Anti-androgens	GnRH antagonist	Inhibitors of androgen synthesis
BUSERILINE GOSERELIN **LEUPRORELIN** TRIPTORELIN	**Steroidal** CYPROSTERONE ACETATE **Non-steroidal** Bicalutamide Nilutamide flutamide	DEGARELIX	ABITERONE ACETATE

2.3.2. Breast cancer

The presence of receptors must first be demonstrated. This depends on the patient's hormonal conditions. Before the menopause, oestrogens are of ovarian origin (so a

pharmacological castration must be created) and after the menopause, oestrogens are derived from the conversion of androgens (aromatization).

Anti-oestrogens	Aromatase inhibitor
TAMOXIFEN FULVESTRANT	LETROZOLE **ANASTROZOLE** EXEMESTANE

The two most commonly used molecules are TAMOXIFEN and ANASTROZOLE. They should therefore be monitored as a priority.

2.4. Tyrosine kinase inhibitors (TKIs)

TKI tyrosine kinases (TKs) are small molecules that are active in the intracellular environment of target transmembrane receptors.

The main advantage of these drugs is that they are taken orally, which means that they can be treated at home with fewer constraints and risks associated with intravenous administration. They are often not first-line treatments.

- The leader is **IMATINIB**. It is no longer protected by a patent and is on the market as a generic drug. It is essential for the treatment of gastrointestinal stromal tumours (GIST), chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL).

Currently, these molecules are not subject to ruptures of stock, whether they are still protected by a patent (the majority) or are already present as generic drugs. Their usefulness is increasing, particularly because of their use in out- patients. For these medicines, the European challenge is more to **ensure equal access to medicines for all European patients** due to the cost of these treatments.

When the Academy hospital pharmacists in Europe with the help of the EAHP (European Association of Hospital Pharmacists), the TKIs cited as sensitive, as well as molecules already present under generic status such as **IMATINIB, GEFITINIB, ERLOTINIB**, were molecules with recent marketing authorisation, such as: AFATINIB, IBRUTINIB, LORLATINIB, ALECTINIB

List of Inhibitors on the market

DCI	Mode of action	Location of the cancer	Out-patients/hospital
IMATINIB	EGFR inhibitor	GIST, CML, ALL	Out-patients
ERLOTINIB	EGFR inhibitor	NSCLC/pancreas	Out-patients

AFATINIB	EGFR inhibitor	NSCLC	Out-patients
IBRUTINIB	EGFR inhibitor	CLL, mantle cell lymphoma	Out-patients
LORLATINIB	EGFR inhibitor	NSCLC	Out-patients
ALECTINIB	EGFR inhibitor =HER1)	NSCLC ALK	Out-patients
GEFITINIB	EGFR inhibitor	NSCLC	Out-patients
SUNITINIB	Multikinase inhibitor	Advanced kidney in first line	Out-patients
SORAFENIB	Multikinase inhibitor	Advanced kidney/hepatocellular stage Child A	Out-patients
LENALINOMIDE	Anti-TNF alpha	Refractory multiple myeloma	hospital
EVEROLIMUS	Selective m-TOR inhibitor	Kidney	Out-patients
LAPATINIB	TKI	HER2+++ breast	Out-patients
ABIRATERONE	Anti-androgens	prostate	Out-patients
VERUMAFENIB	MPAkinase inhibitor	BRAF-mutated melanoma	Out-patients
CRIZOTINIB	TKI	NSCLC ALK	Out-patients
VANTETANIB	TKI	thyroid	Out-patients
AXITINIB	Multikinase inhibitor	Kidney	Out-patients
REGORAFENIB	Multikinase inhibitor	JRCm	Out-patients
IDELALISIB	PI3K delta inhibitor	LLC	Out-patients
BOSUTINIB	TKI	LMC	Out-patients

– List of acronyms

- NSCLC: Non-small cell lung cancer
- ALK; translocation of the ALK gene
- CLL: chronic lymphocytic leukaemia
- CML: chronic myeloid leukaemia
- ALL: acute lymphoblastic leukaemia
- mRCC: Metastatic Colorectal Cancer
- GIST: gastrointestinal stromal tumour

2.5. immunostimulant: BCG maintenance therapy in superficial bladder tumours.

Since their first use by Morales in 1976, intravesicular bacillus Calmette-Guérin (BCG) instillations have become the gold standard treatment for bladder tumours at high risk of recurrence and progression[6]. In T1G3 tumours, which are the most aggressive, BCG therapy allows a 5-year recurrence-free survival rate of over 80% with bladder preservation.

This BCG is administered directly into the bladder by instillation.

The chronic unavailability of BCG in this form (bladder instillation) is a real public health problem.

The supply of intravesicular BCG was very restricted between 2012 and 2017 due to production problems for the main drug on the market at the time, Immucyst® (Sanofi), and too low a volume of production for the alternatives.

The situation improved in 2017, notably due to the acceleration of production of an alternative to Immucyst®, BCG-Medac®, and the importation of Canadian units of Oncotice®).

Only one laboratory in Europe (MEDAC) currently supplies the entire European market.

The National Academy of Pharmacy considers this fragility of supply to be a cause for concern and suggests that the European Union should develop a strategy to increase the number of operators in this market.

2.6. Arsenic trioxide and ATRA

ARSENIC TRIOXIDE: For the French High Authority for Health (AVIS SUR LES MÉDICAMENTS - - (HAS sept.15, 2017) its clinical interest is important in the treatment of acute promyelocytic leukaemia in combination with **ALL-TRANS-RETINOIC ACID** (ATRA)

The combination of ATRA and arsenic trioxide is a first-line treatment in this indication.

The Academy is concerned about arsenic trioxide, as worldwide demand has been steadily increasing in recent years, due to extensive research in other tumour locations. Particular attention must be paid to securing the supply for the European Union.

3. SUPPORTIVE AND ADJUVANT TREATMENT

3.1. Supportive treatments

As mentioned above, cancer treatments are particularly taxing for patients, who suffer serious side effects. Certain associated drugs must be given in combination with the anti-

[6] Bladder tumours, Immunotherapy, BCG, maintenance treatment. Authors: Michael PEYROMAURE, Marc ZERBIB Reference: Prog Urol, 2004, 14, 105-108

cancer molecules themselves to attenuate their severity and also to facilitate the continuation of the treatment.

Supportive care drugs are used in a variety of situations

SYMPTOMS		MEDICINES
Pain	Pain management (level 2 and 2) Stage 1 or 2 for mucositis	Morphine (**MORPHINE, FENTANYL)**
Alopecia	Highly alopecising drugs: antracyclines (epirubicin, doxorubicin, daunorubicin), taxanes (docetaxel, paclitaxel)	
Muciosal infections	Anticancer drugs involved: cyclophosphamide, taxanes, anthracyclines, methotrexate, 5-FU continuous infusion	Antifungal treatments (fluconazole *per os* 50 to 100mg/d) Antiviral (anti-herpetic) treatments Painkillers
Myelotoxicity	Mechanism: destruction of differentiating haematopoietic stem cells - anaemia, leuconeutropenia - thrombocytopenia	Erythropoietin (=EPO) Darbepoetin Haematopoietic growth factors: G-CSF (granulocyte colony stimulating factor): **FILGRASTIM,** pegfilgrastim, lenograstim
Infections	**Major risk in cancer patients**, especially in case of neutropenia/ Bacterial infections most often (90%): staphylococcus	Broad-spectrum antibiotic therapy
Nausea/vomiting	One of the most feared side effects: almost systematic: early or immediate N/V, delayed, anticipated	**Corticosteroids: DEXAMETHASONE / PREDNISONE / PREDNISOLONE / METHYLPREDNISOLONE** **Dopamine antagonists** Anti-5HT3 = Setrons: **ONDANSETRON**, granisetron, ... Anti-NK1: aprepitant
Skin toxicity		Benzoyl peroxide **DERMOCORTICOIDS** Topical (erythromycin, clindamycin) or oral (doxycycline) TBAs

Urinary toxicity	urinary toxicity risks of oxazaphosphorines	**MESNA (UROMITEXAN®)** is used in the management of
Other toxicity		Folinic salvage (**CALCIUM FOLINATE)**

3.2. Adjuvant treatment

CALCIUM FOLINATE :

- Increased cytotoxicity of fluorouracil. Disodium folinate potentiates the action of fluorouracil used in the palliative treatment of colorectal carcinoma.
- Prevention of methotrexate-induced toxicity. Disodium folinate is used to reduce toxicity and counteract the action of folic acid antagonists, such as methotrexate. This procedure is known as folinic rescue.

4. EXAMPLES OF WIDELY USED PROTOCOLS

- Example of the **FEC 50, 75, or 100** protocol: D1 to D21, 3 or 4 cycles followed by 3 or 4 cycles of docetaxel (Taxotere®) - in breast cancer

	FEC 100	D (mg/m2)	Track
F	FLUOROURACIL	500	20 min IV infusion
E	**EPIRUBICIN**	50, or 75, or 100	20 min IV infusion
C	CYCLOPHOSPHAMIDE	500	20 min IV infusion

- Example of **FOLFOX4 FOLINATE** Fluorouracil **OXALIPLATIN** = D1 - D14, 6 cycles minimum in adjuvant and metastatic colorectal cancer, in locally advanced or metastatic gastric cancer, in locally advanced or metastatic esophageal cancer

5. CHECKLIST

THE MOLECULES THAT ARE PARTICULARLY USED IN TERMS OF VOLUME ARE SHOWN IN RED.

NEARLY "ORPHAN" MOLECULES ARE SHOWN IN GREEN

DCI	rational/ rationale
ADRIAMYCIN	Essential: present in many protocols e.g. Breast (FAC protocol) - haematological cancers (substitutable with epirubicin)
Anastrozole	Indispensable in hormone-dependent breast cancer in postmenopausal women - in many reference protocols
ATRA/all-trans-retinoic acid	Essential in some haematological cancers
azacitidine	Essential in haematology Acute leukaemia and myelodysplastic syndrome (AML) - attention to current tension in the USA
BCG (intravesical instillation)	One of the two essential medical treatments for bladder cancer (*in situ*) - together with mitomycin (both intravesical, in case of rupture remaining solution = cystectomy) - only one manufacturer in Europe MEDAC
bendamustine	Essential in haematology: LLEC first-line, myeloma first-line and as an alternative to marrow transplantation and for certain patients for whom thalidomide is contraindicated and LMNH if rituximab fails
bleomycin	Essential in several protocols for curable cancers e.g. curable testicular cancer in young subjects (BEP protocol) and ABVD protocol in lymphoma
busulfan	Indispensable: limited but essential in pre-transplant conditioning of haematopoietic stem cells
capecitabine	Essential: oral alternative to 5 FU, included in simplified protocol for digestive and breast cancer
carboplatin	Indispensable: used in ovarian, head/neck, small cell bronchial cancer protocols and especially involved in several treatments of rare paediatric cancers, retinoblastoma, neuroblastoma, Wilmes tumour
carmustine (BICNU)	Indispensable in many haematological indications (many protocols): multiple myeloma and L Hodgkin and LMNH
chlorambucil	Essential: used in LLC maintenance and small LLC
chlormethine/metchlorethamine	ATTENTION Almost untraceable, cyclophosphamide substitution in Hodgkin = but 30% loss of chance of cure for a curable cancer!
CISPLATIN	Indispensable in many cancers - many protocols in upper GI cancers (esophagus/stomach), in NAPC bronchial cancer and head/neck cancer + BEP reference treatment (testis)
cladribine	Indispensable in haematology and almost an orphan
Corticosteroids	FUNDAMENTAL: Several products: dexamethasone, hydrocortisone, prednisone. Essential: chemo (haematology); chemically induced vomiting treatments
CYCLOPHOSPHAMIDE	Indispensable in many cancers - breast - FEC/FAC protocol - haematology protocols + basis for treatment of many sarcomas - little research AC protocol)

cytarabine	Indispensable induction protocol for AML and prevention of meningeal relapse of AML and ALL - intrathecal) product formulation problem - very viscous - hydrophobic - difficult to manufacture
dacarbazine	Essential in Dermatological Cancers (almost orphan)
dactinomycin	Indispensable used in paediatric cancers
daunorubicin	Indispensable quasi-orphan - AML induction protocol
docetaxel	Indispensable for many cancers - ex-breast cancer -+ lung cancer - non-small cell, gastric cancer - in prostate - reference product in prostate - widely used in France
DOXORUBICIN = ADRIAMYCIN	Indispensable in many cancers
EPIRUBICIN	Indispensable in many cancers; e.g. in breast cancer -FEC) less cardiotoxic than doxorubicin
erlotinib	in the CBNAC and in the pancreatic cancer
etoposide	Indispensable Major product: many haematology protocols, part of the reference protocol for curable testicular cancer
fludarabine	Indispensable LLC interest oral form allows out-patient chemotherapy-few industrial operators *a priori*
FLUOROURACIL(5-FU)	Essential in many multi-drug cancers - reference treatment - examples: digestive cancer FOLFOX FOLFIRI protocol, breast cancer (FEC)
gemcitabine	Indispensable, major in pancreatic (reference treatment) + other cancers (breast, etc.)
hydroxycarbamide/hydroxyurea	essential in myeloproliferative syndrome - and very important in sickle cell disease
idarubicin	Essential: near orphan - haematology - oral form
IFOSFAMIDE	Indispensable, similar to cyclophosphamide: numerous high dose protocols in sarcoma (osteosarcoma)
Imatinib	Essential : newly genericized - essential in the treatment of GIST and CML + ALL
irinotecan	Indispensable : colorectal cancer, alternative to oxaliplatin (FOLFOX)
Leuprorelin	Essential hormone therapy ,hormone-dependent prostate cancer
lomustine (UNFC)	Indispensable quasi-orphan - haematology - and brain tumours - oral chemo)
melphalan	Essential in myeloma and especially in transplant conditioning
mercaptopurine	Essential: quasi-orphan/ induction and maintenance chemotherapy AML/ANL
Mesna	Essential to prevent haemorrhagic cystitis in treatment with cyclophosphamide and high-dose ifosfamide
methotrexate	Indispensable in medium-dose protocols for osteosarcoma and lymphoma, and Hodgkin's disease
mitomycin	Indispensable quasi-orphan (rupture + BCG rupture = no more medical treatment bladder cancer

mitoxantrone	Indispensable, almost an orphan drug. The problem of price applies to this type of drug
Morphine	Essential in all advanced cancers
Nivolumab	Essential in many cancers -melanoma, lung etc. Treatment in many protocols
oxaliplatin	Essential in many digestive (colorectal) cancers (FOLFOX)
PACLITAXEL	Essential in many cancers - e.g. breast - ovarian -+ lung non-small cell, gastric cancer
pemetrexed	Essential for bronchial and brain cancers: reference treatment for mesothelioma
pipobroman	Indispensable and almost orphaned
procarbazine	Essential in Hodgkin's lymphoma - reference treatment Hodgkin - MOPP protocol
Rituximab	Indispensable - indispensable in haematology R-CHOP- Several biosimilars
Tamoxifen	Essential in hormone-dependent breast cancer in non-menopausal women
Temozolomide	Essential in glioblastoma
thioguanine 1	maintenance treatment of ALL (especially in paediatrics)
thiotepa	Indispensable and almost orphaned
topoecan	Essential in ovarian/uterine cancer
Trastuzumab	Essential in HER2-expressing breast cancer
arsenic trioxide	Indispensable in haematology for certain specific leukaemias - attention to growing world demand as many research projects are being carried out in other tumour locations - complicated supply chain
vinblastine	Indispensable: included in many reference protocols MOPP, breast, etc.
VINCRISTINE	Essential: in many reference protocols MOPP, breast, etc. lymphoma, Leukaemia (protocol) LAL VP
vindesin	