REGULATORY INFORMATION
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

REGULATORY INFORMATION - CANCER MEDICINES

Summary of regulatory status of the medicines
As recommended in the EML Secretariat’s instructions regarding applications for the addition of new medicines on the WHO Model List of Essential Medicines, the following document gathers information about the regulatory status of selected medicines in the USA, from the US Food and Drug Administration (FDA), and in Europe, including from the European Medicines Agency (EMA). This summary also specifies the indications that the medicine is licensed for by the FDA or the EMA. Finally, information about the patent status of the medicines is also provided for indicative purposes based on the FDA Orange Book and other publicly available information. All information concerns adults unless specified otherwise.

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AFATINIB

Afatinib has been granted regulatory approval in the USA by the FDA on July 12, 2013 (Gilotrif®) (1). In the European Union, afatinib has been granted a marketing authorization through the centralized procedure (EMA) on September 25, 2013 (Giotrif®) (2).

Indications – USA (FDA):
“Gilotrif® is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test”. Limitation of Use: Safety and efficacy of Gilotrif have not been established in patients whose tumors have other EGFR mutations”

Patent status: In the USA, patents on afatinib will expire in 2018 and 2029 (FDA Orange Book).

AFLIBERCEPT - (ziv-aflibercept)

Afibercept (ziv-aflibercept, Injection for Intravenous Infusion) has been granted regulatory approval in the USA by the FDA on August 3, 2012 (Zaltrap®) (1). In the European Union, aflibercept has been granted a marketing authorization through the centralised procedure (EMA) on February 1st, 2013 (Zaltrap®) (2).

Indications - USA (FDA):
“Zaltrap®, in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.”

Patent status: In the USA, the compound patent is estimated to expire in 2020 (information to be confirmed).

AROMATASE INHIBITORS

Anastrozole

Anastrozole has been granted regulatory approval by the FDA in 1995 (Arimidex®) (1). It is also approved in European countries (via national procedures), as well as in Australia and Canada.

Indications - USA (FDA):
“Anastrozole (Arimidex®) is an aromatase inhibitor indicated for:
• Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer (1.1)
• First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer (1.2)
• Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to Arimidex (1.3)”

Patent status: Anastrozole is off patent in the USA and in Europe. Generic versions have been granted regulatory approvals both in the USA and European countries.
Anastrozole (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, USA, Venezuela.

**Letrozole**

Letrozole has been granted initial regulatory approval by the FDA in 1997 (Femara®) (1). It is also authorized in Europe via national procedures, as well as in Australia and Canada.

**USA (FDA):**

“Letrozole (Femara®) is an aromatase inhibitor indicated for:

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer;
- Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy;
- First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer. “

**Patent status:** Letrozole is off patent in the USA and in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

Letrozole (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, UK, Ukraine USA, Venezuela

**Exemestane**

Exemestane has been granted regulatory approval in the USA by the FDA on October 21, 1999 (Aromasin®) (1). Exemestane is also approved in Europe via national procedures as well as in Australia and Canada.

**Indications - USA (FDA):**

“Exemestane (Aromasin®) is an aromatase inhibitor indicated for:

- adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy
- treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.”

**Patent status:** Exemestane is off patent in the USA (FDA orange book) and in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

Exemestane (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina Australia Austria Belgium Brazil Canada Chile China Czech Republic Denmark Finland France Germany Greece Hong Kong Hungary Indonesia Israel Italy Malaysia Mexico Netherlands New Zealand Norway
BENDAMUSTINE

Bendamustine hydrochloride has been granted regulatory approval in the USA by the FDA initially on March 20, 2008 (Treanda®) (1). It has also been approved in Europe via national procedures (Levact®).

Indications – USA (FDA):
“TREANDA is an alkylating drug indicated for treatment of patients with:

- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. (1.1)
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. (1.2).”

Patent status: In the USA, according to the FDA Orange book, patents on bendamustine are due to expire in 2026, 2029 and 2030.

BEVACIZUMAB

Bevacizumab has been granted regulatory approval in the USA by the FDA initially on February 26, 2004 (Avastin®) (1). It has also been approved in Europe through the centralised procedure (EMA) on January 12, 2005 (Avastin®) (2).

Indications - USA (FDA):
“Bevacizumab (Avastin®) is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin containing regimen. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. (1.3)
  - Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. (1.5)
- Metastatic renal cell carcinoma with interferon alfa (1.4)

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)”

Patent status: In the USA, the patent on bevacizumab is expected to expire in 2019.

BICALUTAMIDE
Bicalutamide has been granted regulatory approval in the USA by the FDA initially on October 5, 1995 (Casodex®) (1). It is also approved in European countries through national procedures.

**Indications - USA (FDA):**
“Bicalutamide (Casodex®) 50 mg is an androgen receptor inhibitor indicated for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analog for the treatment of Stage D2 metastatic carcinoma of the prostate.”

**Patent status:** Bicalutamide is off patent in the USA (FDA orange book) and in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

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**CAPECITABINE**

Capecitabine has been granted regulatory approval in the USA by the FDA on April 30, 1998 (Xeloda®) (1). Capecitabine is also approved in Europe through the centralized procedure (EMA) since 2001, as well as in Canada since 1998 and in Australia since 2000.

**Indications - USA (FDA):**
“Capecitabine (Xeloda®) is a nucleoside metabolic inhibitor with antineoplastic activity indicated for:
• Adjuvant Colon Cancer (1.1)
  – Patients with Dukes’ C colon cancer
• Metastatic Colorectal Cancer (1.1)
  – First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred
• Metastatic Breast Cancer (1.2)
  – In combination with docetaxel after failure of prior anthracycline containing therapy
  – As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen “

**Patent status:** In the USA, the key patent on capecitabine (Xeloda®) expired on Dec 14, 2013 (and June 14, 2014 for pediatric indications with data exclusivity until June 10, 2017) (FDA Orange Book). Capecitabine is off patent in European countries since 2013. Regulatory approvals have been granted to generic manufacturers in the USA (FDA) and in Europe (EMA) based on bioequivalence.

Capecitabine (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina Australia Austria Belgium Brazil Canada Chile China Czech Republic Denmark Finland France Germany Greece Hong Kong Hungary India Indonesia Ireland Israel Italy Japan Mexico Netherlands New Zealand Norway Philippines Poland Portugal Russia Singapore South Africa Spain Sweden Switzerland Thailand Turkey UK Ukraine USA Venezuela.

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**CETUXIMAB**

Cetuximab has been granted regulatory approval in the USA by the FDA initially on February 12, 2004 (Erbitux®) (1). In Europe, it has been granted a marketing authorization through the centralized procedure (EMA) on June 29, 2004 (Erbitux®) (2).

**Indications and usage - USA (FDA):**
“Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:
Head and Neck Cancer
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• Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
• Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU. (1.1, 14.1)
• Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

Colorectal Cancer
K-Ras mutation-negative (wild-type), EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests
• in combination with FOLFIRI for first-line treatment,
• in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
• as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. (1.2, 5.7, 12.1, 14.2)

Limitation of Use: Erbitux is not indicated for treatment of K-Ras mutation-positive colorectal cancer. (5.7, 14.2).

Patent status: In the USA, data exclusivity is due to expire in 2016. In Europe, the protection on cetuximab expired in 2014.

CISPLATIN

Cisplatin has been granted regulatory approval in the USA by the FDA initially in 1978 (Platinol®) (1). It is also approved in Europe through national procedures.

Indications - USA (FDA):
“PLATINOL (cisplatin for injection, USP) is indicated as therapy to be employed as follows:
• Metastatic Testicular Tumors
In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.
• Metastatic Ovarian Tumors
In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of PLATINOL and cyclophosphamide. PLATINOL, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received PLATINOL therapy.
• Advanced Bladder Cancer
PLATINOL is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments, such as surgery and/or radiotherapy.”

Patent status: Cisplatin is off patent in the USA (FDA Orange Book) as well as in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

CRIZOTINIB

Crizotinib has been granted regulatory approval in the USA by the FDA initially on August 26, 2011 (Xalkori®) (1). It has also been granted a marketing authorization in Europe through the centralized procedure (EMA) on October 23, 2012 (Xalkori®) (2).

Indications – USA (FDA):
“XALKORI® is a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.”

**Patent status:**
In the US, patents on crizotinib are due to expire from 2025 (FDA Orange Book). In Europe, the patent is due to expire in 2025.

### DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION

Doxorubicin Hydrochloride Liposome Injection for intravenous infusion has been approved in the USA by the FDA in November 17, 1995 (Doxil®) (1). The pegylated liposome formulation of doxorubicin also obtained a marketing authorization in Europe in 1996 (Caelyx®).

**Indications - USA (FDA):**
“DOXIL® is an anthracycline topoisomerase inhibitor indicated for:

- **Ovarian cancer** (1.1)
- After failure of platinum-based chemotherapy.

- **AIDS-related Kaposi’s Sarcoma** (1.2)
- After failure of prior systemic chemotherapy or intolerance to such therapy.

- **Multiple Myeloma** (1.3)
- In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.”

**Patent status:** According to the FDA Orange Book, there are no unexpired patents for Doxorubicin Hydrochloride Liposome Injection in the USA.

### ERLOTINIB

Erlotinib hydrochloride has been granted regulatory approval in the USA by the FDA on November 18, 2004 (Tarceva®) (1). It has also been approved in Europe through the centralised procedure (EMA) on September 19, 2005 (Tarceva®) (2).

**Indications and usage - US (FDA):**
“Erlotinib hydrochloride (Tarceva®) is a kinase inhibitor indicated for:

- **First-line treatment** of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. (1.1)

- **Maintenance treatment** of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)

- **Treatment of locally advanced or metastatic NSCLC** after failure of at least one prior chemotherapy regimen. (1.1)

- **First-line treatment** of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. (1.2)

**Limitations of Use:**
- **TARCEVA is not recommended** for use in combination with platinum-based chemotherapy.
- **Safety and efficacy** of TARCEVA have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21(L858R) substitution.”
**FILGRASTIM**

FILGRASTIM has been granted regulatory approval in the USA by the FDA initially on February 20, 1991 (Neupogen®) (1). It is also approved in European countries through national procedures.

**Indications and usage - US (FDA):**

- Cancer Patients Receiving Myelosuppressive Chemotherapy
- Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation
- Chemotherapy
- Cancer Patients Receiving Bone Marrow Transplant
- Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy
- Patients With Severe Chronic Neutropenia

**Patent status:** In the US, the compound patent on filgrastim (Neupogen®) expired in December 2013. In Europe, filgrastim (Neupogen®) is off patent since 2006. Biosimilar versions of filgrastim have been approved by the EMA.

**FLUDARABINE**

FLUDARABINE has been granted regulatory approval in the USA by the FDA initially on April 18, 1991 (1). It is also approved in European countries through national procedures.

**Indications and usage - US (FDA):**

“Fludarabine Phosphate Injection is a nucleotide metabolic inhibitor indicated for:

The treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naive or non-refractory CLL patients is not established.”

**Patent status:** Fludarabine phosphate is off patent in the USA (FDA Orange Book) as well as in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

Fludarabine phosphate (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina Australia Austria Belgium Brazil Canada Chile China Denmark France Germany Greece Hong Kong Hungary India Italy Malaysia Mexico Netherlands New Zealand Philippines Poland Portugal Russia Singapore South Africa Spain Sweden Switzerland Thailand Turkey UK USA Venezuela.

**GEFITINIB**

GEFITINIB was approved in the USA by the FDA on May 5, 2003 (Iressa®) but was later discontinued (1, 2). In Europe, Gefitinib has been granted a marketing authorisation through the centralised procedure (EMA) on June 24, 2009 (Iressa®) (3).
**Indications - EU (EMA):**
“IRESSA is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.”

**Patent status:** In the USA, the patent on Gefitinib is due to expire in May 2017 (FDA Orange Book – Discontinued drug product). In Europe, the patent on Gefitinib is due to expire in 2016 and supplementary protection certificates have been granted in a number of countries until 2019.

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**GEMCITABINE**

Gemcitabine Hydrochloride has been granted regulatory approval in the USA by the FDA on May 15, 1996 (Gemzar®) (1). It is also approved in European countries through national procedures.

**Indications - USA (FDA):**
“Gemcitabine (Gemzar®) is a nucleoside metabolic inhibitor indicated:
- in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy (1.1)
- in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated (1.2)
- in combination with cisplatin for the treatment of non-small cell lung cancer (1.3)
- as a single agent for the treatment of pancreatic cancer (1.4)”

**Patent status:** Gemcitabine is off patent in the USA (FDA orange book) and in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

Gemcitabine (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina Australia Austria Belgium Brazil Canada Chile China Czech Republic Denmark Finland France Germany Greece Hong Kong Hungary India Indonesia Ireland Israel Italy Malaysia Mexico Netherlands Norway Philippines Poland Portugal Russia Singapore South Africa Spain Sweden Switzerland Thailand Turkey UK Ukraine USA Venezuela

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**IDARUBICIN**

Idarubicin Hydrochloride has been granted regulatory approval in the USA by the FDA initially in 1990 and in its current form on February 17, 1997 (Idamycin PFS®) (1). It is also approved in European countries through national procedures.

**Indications - USA (FDA):**
Idarubicin Hydrochloride (Idamycin PFS®) Injection in combination with other approved antileukemic drugs is indicated for the treatment of acute myeloid leukemia (AML) in adults.

**Patent status:** Idarubicin Hydrochloride is off patent in the USA (FDA orange book) and in European countries where generic versions have been granted regulatory approvals based on bioequivalence.

Idarubicin Hydrochloride (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina Australia Austria Belgium Brazil Canada Chile China Czech Republic Denmark Finland France Greece Hong Kong Hungary Ireland Israel Italy Malaysia Mexico Netherlands New Zealand Norway
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Philippines Poland Portugal Russia Singapore South Africa Spain Sweden Switzerland Thailand Turkey UK Ukraine USA Venezuela

IMATINIB

Imatinib (imatinib mesylate) has been granted regulatory approval by the FDA in 2001 (Gleevec®) [1]. Imatinib has also been granted a marketing authorization in Europe through the centralized procedure (EMA) (Glivec®) in 2001. Imatinib is currently approved in over 110 countries for the treatment of both haematological malignancies and solid tumours.

Indications - USA (FDA):
“Gleevec is a kinase inhibitor indicated for the treatment of:
• Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (1.1)
• Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy (1.2)
• Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3)
• Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy (1.4)
• Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements (1.5)
• Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown (1.6)
• Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1PDGFRαfusion kinase negative or unknown (1.7)
• Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
• Patients with Kit (CD117) positive un resectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) (1.9)
• Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST (1.10)”

Patent status: In the USA, according to the FDA Orange book, the original compound patent will expire on January 4, 2015. In Europe, the patent expired in March 2013. However, in certain European countries, supplementary protection certificates (SPC) have been granted, protecting imatinib from generic competition until 20 June 2016 (e.g. UK).

Since 2013, marketing authorisations for generic versions of imatinib (100 mg and 400 mg forms) have been granted in Canada (Teva, Apotex, Actavis) as well as in Europe (accord, Teva, Actavis, Medac).

Imatinib (branded and generic) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina, India, Canada, South Africa, USA, Netherlands, Australia, Austria, Belgium, Brazil, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, Mexico, New Zealand, Netherlands, Norway, Philippines, Poland, Portugal, Russia, Singapore, Spain, Sweden, Switzerland, Thailand, Turkey, UK, Ukraine, Venezuela.
IRINOTECAN

Irinotecan has been granted regulatory approval in the USA by the FDA initially in 1996 (Camptosar®) (1). It is also approved in Europe through national procedures.

Indications – USA (FDA):
“[Irinotecan (Camptosar®)] is a topoisomerase inhibitor indicated for:
• First-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum.
• Patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.”

Patent status:
In the USA, the compound patent for irinotecan (camptosar®) expired in 2008. According to the FDA orange book, combination patents of irinotecan with 5-fluorouracil and leucovorin are due to expire in 2020. In Europe, the compound patent expired in 2009 and generic versions have been granted regulatory approvals in various European countries based on bioequivalence.

LEUPROLIDE ACETATE

Leuprolide acetate (suspension depot for injection) is approved in the USA by the FDA (Lupron depot®) since 1989 (1). Leuprolide acetate (suspension for subcutaneous injection) (Eligard) is approved by the FDA since 2002 (2). It has also been approved in European countries through national procedures (Eligard®).

Indications – USA (FDA):
“LUPRON DEPOT® is a gonadotropin releasing hormone (GnRH) agonist indicated for:
• palliative treatment of advanced prostatic cancer.”

“ELIGARD® is a gonadotropin releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer”

Patent status: In the USA, according to the FDA Orange Book, the key patents on leuprolide acetate (Lupron Depot®) expired. A patent on “release microspheres and preparation of thereof” will expire in 2016. According to the FDA Orange Book, the first patent on Eligard® expired but other patents might impede generic competition until March 2020.

MELPHALAN

Melphalan has been approved in the USA by the FDA (Alkeran®) (1) as well as in European countries through via national procedures.

Indications – USA (FDA):
“ALKERAN Tablets are indicated for the palliative treatment of multiple myeloma and for the palliation of non-resectable epithelial carcinoma of the ovary.”

Patent status: Melphalan is off patent in the USA (FDA Orange Book).
MURAMYL TRIPEPTIDE – MTP - MIFAMURTIDE

Mifamurtide has been granted a marketing authorization in the European Union (centralized procedure – EMA) on March 6, 2009 (Mepact®) (1). It is not approved in the USA by the FDA.

Indications – EU (EMA):
“MEPACT is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.”

Patent status: According to available information, it seems that the patent on mifamurtide was due to expire in 2010 in the USA (information to be completed).

PANITUMUMAB

Panitumumab has been granted regulatory approval in the USA by the FDA initially on September 27, 2006 (Vectibix®) (1). In Europe, it has been granted a marketing authorization through centralized procedure (EMA) on December 3, 2007 (Vectibix®) (2).

Indications – USA (FDA):
“Panitumumab (Vectibix®) is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type KRAS (exon 2) metastatic colorectal cancer (mCRC) as determined by an FDA-approved test for this use:
• In combination with FOLFOX for first-line treatment. (1.1, 14.2)
• As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. (1.1, 14.1)
• Limitation of Use: Vectibix is not indicated for the treatment of patients with KRAS-mutant mCRC or for whom KRAS mutation status is unknown. (1.2, 2.1, 5.2, 12.1)”

Patent status: According to available information, in the USA, the key patent on panitumumab is due to expire in 2017 (extension until 2020). In Europe, the patent is due to expire in 2018, with SPCs having been granted in a number of European countries until 2022 (information to be completed).

PEMETREXED

Premetrexed has been granted regulatory approval in the USA by the FDA initially in 2004 (Alimta®) (1). In the European Union, premetrexed has also been granted a marketing approval (EMA – centralised procedure) on September 20, 2004 (Alimta®)(2).

Indications – USA (FDA):
“ALIMTA® is a folate analog metabolic inhibitor indicated for:
• Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer:
  • Initial treatment in combination with cisplatin. (1.1)
• Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.2)
  • After prior chemotherapy as a single-agent. (1.3)
  • Mesothelioma: in combination with cisplatin (1.4)
Limitations of Use:
ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. (1.5)"

Patent status: In the USA, patent protection on premetexed is due to expire in 2016. In Europe, the basic compound patent expired, with SPCs having been granted in various European countries until December 2015.

REGORAFENIB

Regorafenib has been granted regulatory approval in the USA by the FDA initially in 2012 (stivarga®, tablets for oral use) (1). In Europe, a marketing authorization has been granted by the EMA in 2013 (stivarga®) (2).

Indications – USA (FDA):
“Regorafenib (Stivarga®) is a kinase inhibitor indicated for the treatment of patients with:
• Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. (1.1)
• Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. (1.2)”

Patent status: In the USA (FDA Orange Book), patents on regorafenib are due to expire from 2020.

RITUXIMAB

Rituximab has been granted regulatory approval in the USA by the FDA initially in 1997 (Rituxan®) (1). It has also been granted approval in Europe (EMA) (2) and in Australia (TGA) (Mabthera®) (3) in 1998, as well as in Canada (Rituxan®) in 2000 (4). Rituximab is approved in more than 102 countries worldwide.

USA (FDA)
“Rituximab is indicated for the treatment of patients for the following therapeutic indications:
1.1. Non-Hodgkin’s Lymphoma (NHL):
• Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
• Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
• Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
• Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
1.2. Chronic Lymphocytic Leukemia (CLL)
• Rituxan® (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.”
Other indications: Rituximab is also indicated for the treatment of Rheumatoid Arthritis (RA) as well as for Granulomatosis with Polyangiitis (GPA).

Patent status: In the USA, the key patent on rituximab (Rituxan®) will expire on April 7, 2015. In Europe, the key patent on rituximab (Mabthera®) expired on November 21, 2013. Biosimilars of rituximab have been approved in other jurisdictions, including India in 2007 (Reditux® manufactured by Dr Reddy's Laboratories).

Rituximab is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Argentina, Australia, Austria, Belgium, Brazil, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, New Zealand, Netherlands, Norway, Philippines, Poland, Portugal, Russia, South Africa, Singapore, Spain, Sweden, Switzerland, Thailand, Turkey, UK, Ukraine, Venezuela, Japan, USA, Canada.

**SUNITINIB**

Sunitinib malate has been granted regulatory approval in the USA by the FDA in 2006 (Sutent®, capsules, oral) (1). In Europe, a marketing authorization has been granted through the centralized procedure (EMA) in 2006 (Sutent®) (2).

Indications – USA (FDA):
“Sunitinib (Sutent®) is a kinase inhibitor indicated for the treatment of:
- Gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.
- Advanced renal cell carcinoma (RCC).
- Progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.”

Patent status: In the USA (FDA Orange Book), patents on sunitinib will expire in February 2021 and December 2020.

**THIOTEPA**

Thiotepa is approved in the USA by the FDA (initially in 1994 then re-registered in 2001 under the name Thiotepa) (1). In Europe, Thiotepa has also been granted a marketing authorization through the centralised procedure (EMA) on May 6, 2010 (Tepadina®) (2).

Indications – USA (FDA):
“Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:
- adenocarcinoma of the breast
- adenocarcinoma of the ovary
- for controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities
- for the treatment of superficial papillary carcinoma of the urinary bladder

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin’s disease.”
**Indications - EU (EMA):**

“In combination with other chemotherapy medicinal products:
1) with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;
2) when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.”. It is proposed that Tepadina must be prescribed by physicians experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation.”

**Patent status:** According to the FDA Orange Book, there are no unexpired patents on thiotepa.

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**TRASTUZUMAB**

The first marketing authorization for trastuzumab was granted in the United States of America (FDA) in 1998 (1) (Herceptin®). It is also approved in the EU (EMA) in 2000 (2). Trastuzumab is currently approved in over 120 countries globally.

**US (FDA):**

1.1. Adjuvant Breast Cancer
Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

1.2. Metastatic Breast Cancer
Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

1.3 Metastatic Gastric Cancer
Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

**Patent status:** In the USA, the key patent on trastuzumab (herceptin®) will expire on June 18, 2019. In Europe, the key patent expired in 2012 and supplementary protection certificates (SPC) granted by countries (e.g. UK) expired on June 28, 2014.

Trastuzumab (Herceptin) is reported to be currently registered for sale in the following countries (Source: Martindale: The Complete Drug Reference. 38th ed., 2014): Japan, USA, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, New Zealand, Netherlands, Norway, Philippines, Poland, Portugal, Russia, South Africa, Singapore, Spain, Sweden, Switzerland, Thailand, Turkey, UK, Ukraine, Venezuela.
**TRETINOIN – all-trans retinoic acid (ATRA)**

Tretinoin (all-trans retinoic acid – ATRA) was approved by the FDA on Nov 22, 1995 (Vesanoid® – marketing discontinued – now available under the name Tretinoin – ANDA 77-684). Tretinoin is also approved in European countries through national procedures (Vesanoid®).

**Indications – USA (FDA):**

“VESANOID (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. VESANOID is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with VESANOID.“

**Patents status:** According to the FDA Orange Book, there are no unexpired patents on tretinoin, capsules 10mg.

**VINORELBINE**

Vinorelbine Tartrate has been granted regulatory approval in the USA by the FDA initially on Dec 23, 1994 (Navelbine®) [1]. It is also approved in European countries through national procedures.

**Indications – USA (FDA):**

“Vinorelbine Tartrate (Navelbine®) is a vinca alkaloid indicated:

- In combination with cisplatin for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)
- As a single agent for first-line treatment of patients with metastatic NSCLC."

**Patent status:** Vinorelbine is off patent in the USA (FDA Orange Book) and in European countries where generic versions have been granted regulatory approvals based on bioequivalence.
<table>
<thead>
<tr>
<th>Medicine *not on the WHO Model EML 2013</th>
<th>US brandnames (NCI Drug Dictionary)</th>
<th>PATENT STATUS IN THE UNITED STATES Sources: FDA Orange book / internet search, patent USPTO</th>
<th>PATENT STATUS IN EUROPEAN COUNTRIES Sources: EPO, UK and IE IPO for SCP</th>
<th>EMA status - Generics / Biosimilars marketing authorization (Or, decentralised procedure=availability of generics in France)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aflibercept</strong>*</td>
<td>Zaltrap</td>
<td>Not in FDA Orange Book</td>
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<tr>
<td><strong>Alloprimorol</strong></td>
<td>Zyloprim</td>
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<tr>
<td><strong>Anastrozole</strong>*</td>
<td>Arimidex</td>
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<td>2011</td>
<td>OFF</td>
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<tr>
<td><strong>Letrozole</strong>*</td>
<td>Femara</td>
<td>OFF</td>
<td>2011</td>
<td>OFF</td>
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<tr>
<td><strong>Exemestane</strong>*</td>
<td>Aromasin</td>
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<td>OFF</td>
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<td><strong>Asparaginase</strong></td>
<td>Elspar</td>
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<tr>
<td><strong>Bendamustine</strong>*</td>
<td>Treanda, Levact</td>
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<tr>
<td><strong>Bicalutamide</strong>*</td>
<td>Casodex</td>
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<tr>
<td><strong>Bleomycin</strong></td>
<td>Blenoxane</td>
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<td>Wellcovorin</td>
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<td><strong>Chlorambucil</strong></td>
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<tr>
<td><strong>Crizotinib</strong>*</td>
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<tr>
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<td><strong>Cytarabine</strong></td>
<td>Cytosar-U, Tarabine PF</td>
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<td><strong>Dacarbazine</strong></td>
<td>DTIC-Dome</td>
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<tr>
<td>Medicine *not on the WHO Model EML 2013</td>
<td>US brandnames (NCI Drug Dictionary)</td>
<td>PATENT STATUS IN THE UNITED STATES Sources: FDA Orange book / internet search, patent USPTO</td>
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<td>PATENT STATUS IN EUROPEAN COUNTRIES Sources: EPO, UK and IE IPO for SCP</td>
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<td>Dactinomycin</td>
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<td>Daunorubicin</td>
<td>Rubidomycin</td>
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<td></td>
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<td>Taxotere</td>
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<td>Doxorubicin Hydrochloride Liposome Injection*</td>
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<td>Etoposide</td>
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<td>Filgrastim*</td>
<td>Neupogen</td>
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<td>Expiry date</td>
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<td>Fludarabine*</td>
<td>Fludara</td>
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<td>Hydroxyurea/hydroxycarbamide</td>
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<td>Ifosfamide</td>
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<td>Irinotecan*</td>
<td>Camptosar</td>
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Notes:
- **Expiry date**: Includes information on Supplementary Protection Certificates (SPCs).
- **EMA status**: Generics / Biosimilars marketing authorization (Or, decentralised procedure=availability of generics in France).
- **Data exclusivity**: Jan 25, 2016.
<table>
<thead>
<tr>
<th>Medicine</th>
<th>US brandnames (NCI Drug Dictionary)</th>
<th>PATENT STATUS IN THE UNITED STATES Sources: FDA Orange book / internet search, patent USPTO</th>
<th>PATENT STATUS IN EUROPEAN COUNTRIES Sources: EPO, UK and IE IPO for SCP</th>
<th>European countries - regulatory approvals of generic versions</th>
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<tbody>
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<td>Patent status (compound patent) ON/OFF</td>
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<td>Meplalan*</td>
<td>Alkeran</td>
<td>FDA Orange Book: &quot;No unexpired patent for this product&quot;</td>
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<td>Mercaptopurine</td>
<td>Purinethol, Purixan</td>
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<td>Methotrexate</td>
<td>Intrexate, Folex Mexat</td>
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<td>Pemetrexed*</td>
<td>Alimta</td>
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<td>US5344932 - July 24, 2016 (Ped exclusivity 2017)</td>
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<td>Hydeltra, Hydeltrasol</td>
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<td>Procainamide</td>
<td>Motulane</td>
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<td>Regorafenib*</td>
<td>Stivarga</td>
<td>ON</td>
<td>US7351834 Due to expire on Jan 12, 2020 US8680124 (Treatment of cancers with acquired resistance to kit inhibitors) - 2028 US8637553 - 2029</td>
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<td>Rituximab*</td>
<td>Rituxan</td>
<td>ON</td>
<td>Key patent: US736137 - April 7, 2015</td>
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<td>Sunitinib*</td>
<td>Sutent</td>
<td>ON</td>
<td>US6573293 and US7125905 - due to expire on Feb 15, 2021 US7211600 = due to expire on Dec 22, 2020</td>
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<td>Tamoxifen</td>
<td>Nolvadex</td>
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<td>Old brand thioguanine</td>
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<td>Thiopen (US), Tepadina (EU)</td>
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</tbody>
</table>

Notes: *not on the WHO Model EML 2013
<table>
<thead>
<tr>
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<th>European countries - regulatory approvals of generic versions</th>
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<td><strong>Tretinoin</strong></td>
<td>Tretinoin, Vesanoid</td>
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<td>Vinblastine</td>
<td>Velban Velsar</td>
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<td>Vincristine</td>
<td>Vincasar</td>
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<tr>
<td>Vinorelbine</td>
<td>Navelbine</td>
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