

Marketing Authorisations under Exceptional Circumstances for Oncology Drugs

An analysis of approval and
reimbursement decisions of
four drugs



Ludwig Boltzmann Institut
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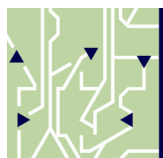
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List of Abbreviations

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ASMR	Amélioration du Service Médical Rendu
BMF	Berlin-Frankfurt-Münster
BMT	Bone marrow transplant
BSC	Best Supportive Care
CED	Coverage with Evidence Development
CFH	Commissie Farmaceutische Hulp/Committee Pharmaceutical Aid
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
CTC	Conditional Treatment Continuation
CVZ	College voor Zorgverzekeringen
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EORTC STBSG	European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group
EPAR	European Public Assessment Report
HAS	Haute Autorité de Santé
HDC	Histamine Dihydrochloride
HSCT	Hematopoietic Stem Cell Transplant
ICER	Incremental Cost-Effectiveness Ratio
IL-2	Interleukin-2
LBL	Lymphoblastic Lymphoma
LFS	Leukaemia Free Survival
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OS	Overall Survival
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
QALY	Quality adjusted life-year
RIZIV	Rijks Instituut voor Ziekte – en Invaliditeits Verzekering
SCT	Stem Cell Transplant
SMC	Scottish Medicines Consortium
SMR	Service Médical Rendu
STS	Soft Tissue Sarcoma
TTP	Time To Progression
VWS	Health, Welfare and Sports

Summary

Background

Orphan drug regulation was created out of the idea that patients suffering from rare conditions should be entitled to the same quality of treatment as other patients. Some conditions however, are so rare that a thorough clinical development programme, normally required, is practically impossible. In these cases the European Medicines Agency (EMA) can authorise a drug under exceptional circumstances.

background

Aim and research questions

This report aims to provide insight into the authorisation under exceptional circumstances of oncology drugs. We try to answer the following questions:

aim and research questions

- ✧ What clinical data were presented by the applicant and what were the considerations by the Committee for Medicinal Products for Human Use (CHMP) for granting exceptional circumstances?
- ✧ What were the additional requirements to be fulfilled by the marketing authorisation holder?
- ✧ What additional data became available on the originally licenced indication and did it confirm the initial expectations?
- ✧ How do reimbursement agencies assess these drugs?
- ✧ Are there any patient access schemes for these drugs?
- ✧ Do the patients have access to the drugs?

Methods

This report considered oncology drugs currently licenced under exceptional circumstances. Reimbursement agencies from England, Scotland, Belgium, France and the Netherlands were included. A MEDLINE-search for literature was performed through Pubmed and grey literature was included from EMA and the reimbursement agencies.

methods

Results

Four oncologic drugs are currently licensed under exceptional circumstances; clofarabine, nelarabine, trabectedin and histamine dihydrochloride. Histamine dihydrochloride was the only drug tested in a phase III trial. For clofarabine, nelarabine and trabectedin the justification for the authorisation under exceptional circumstances was the small size of the patient population. For histamine dihydrochloride it was unclear. Most of the additional requirements by the CHMP considered safety measures and they were not always completed within the set time-frame.

results

The methods of the reimbursement assessments varied. One patient access scheme was identified for trabectedin in England. Some of the drugs were not accessible in some countries and for others it was unclear.

Conclusion and recommendation

To successfully develop drugs for very rare conditions, it is important that industry, EMA and reimbursement agencies intensify the collaboration. On introduction these drugs cannot always prove their cost-effectiveness, therefore conditional coverage with evidence development, preferably on an international level, should be encouraged and facilitated.

conclusion and recommendations

1 Introduction

Since the founding of the European Medicines Agency (EMA) in 1995, over fifty novel oncologic drugs have reached the European market. Despite advances in the development of cancer drugs in the last decades, there is still a high medical need for curative therapies. To accelerate patient access to new treatments in all fields of medicine and to stimulate research by pharmaceutical companies, the European Commission has laid down multiple regulations concerning marketing authorisation for pharmaceuticals.

rationale for orphan drug regulation

As stated in Regulation (EC) No 141/2000, orphan drug regulation was created out of the idea that patients suffering from rare conditions should be entitled to the same quality of treatment as other patients. The pharmaceutical industry would be unwilling to develop the medicinal product for rare diseases under normal market conditions, because the costs of developing and bringing to the market of such a product would not be recovered by the expected sales [1].

some conditions are too rare for a thorough clinical development programme

Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients, therefore orphan medicinal products are submitted to the normal evaluation process [1]. Some conditions however, are so rare that a thorough clinical development programme, normally required, is practically impossible. In this case it is possible to get a marketing authorisation under exceptional circumstances [2].

no extensive guidelines on exceptional circumstances

There are some possible pitfalls to this policy. There are no extensive guidelines on when exceptional circumstances are applicable, which gives the Committee for Medicinal Products for Human Use (CHMP) freedom to apply them when they think it is appropriate. It also is unclear what the conditions and arguments are to apply this policy and whether they are justified.

lacking of thorough clinical development programme conflicts with quality, safety and efficacy

Secondly, this policy somewhat contradicts the statement that patients with rare diseases deserve the same quality, safety and efficacy in medicinal products as other patients. Especially the latter two aspects could be expected to be less convincing when a thorough clinical development programme is lacking.

more likely to not meet the requirements for reimbursement

Thirdly, it conflicts with the so called 'fourth hurdle' in drug development. To gain market access and reimbursement, the demonstration of clinical- and cost-effectiveness are in some countries a necessity [3, 4]. A limited clinical development programme could possibly not satisfy the requirements for reimbursement. For these reasons, it is thinkable that a marketing authorisation under exceptional circumstances might not always have its desired effect in providing safe and effective medicines to seriously ill patients.

oncology drugs are often without phase III trial

Concerns have been raised by Niraula et al [5] about the safety of newly approved cancer drugs in general. The greater efficacy of these drugs seems to come with an increase in morbidity and treatment-related mortality, owing to the toxicity of the treatments. This may be a consequence of the fact that oncology drugs are often approved without a phase III trial [6] and that the pivotal trial design for orphan oncology drugs, but also for non-orphan oncology drugs, is often far from ideal [7-10].

access to orphan drugs in Europe varies

A study conducted by EURORDIS in 2006 analysed the availability of 21 different orphan drugs in 28 European countries [11]. The results showed that there was a large variation in access to orphan drugs. Only in four coun-

tries nearly all drugs were available to patients. The four oncologic drugs that were assessed in the EURORDIS study were available to around 70 % of the total population included.

In the past decade, a lot of attention has been given to orphan drugs and orphan drug regulation. In this report, we focus explicitly on oncology drugs authorised under exceptional circumstances.

1.1 Aim and objectives

This report aims to provide insight into the authorisation under exceptional circumstances of oncology drugs by exploring the possible pitfalls presented earlier. We try to answer the following questions:

- ✧ What clinical data were presented by the applicant and what were the considerations by the CHMP for granting exceptional circumstances?
- ✧ What were the additional requirements to be fulfilled by the marketing authorisation holder?
- ✧ What additional data became available on the originally licenced indication and did it confirm the initial expectations?
- ✧ How do reimbursement agencies assess these drugs?
- ✧ Are there any patient access schemes for these drugs?
- ✧ Do the patients in the selected countries have access to the drugs?

research questions

1.2 Materials and Methods

Product selection

Drugs licensed under exceptional circumstances were identified via the website of the EMA using the European Public Assessment Report (EPAR) database. Only new chemical or biological entities, currently authorised under exceptional circumstances by the European Commission for anticancer treatment were included. Supportive therapies (e.g. bisphosphonates, immunoglobulins, antiemetics), colony-stimulating factors, chemoprevention treatments, vaccines and generics were excluded. Label extensions obtained after the initial marketing authorisation were not considered.

oncology drugs licenced under exceptional circumstances

Selection reimbursement agencies

The main inclusion criteria for the reimbursement agencies were the existence of publicly available assessment reports in Dutch, English or French and the nationwide reach of their advice. Because this report considers EMA regulation, only European agencies were included. The inclusion of England, Scotland, Belgium, France and the Netherlands was an unsystematic selection.

Belgium, England, France, the Netherlands and Scotland were included

Search strategy

**main sources:
EMA, MEDLINE,
clinicaltrials.gov and
reimbursement agencies**

For the overview of the additional clinical evidence a MEDLINE-search was performed via Pubmed for all clinical studies concerning the original licenced indication. The search terms were the name of the product and the indication. Unpublished studies were identified through regulatory documents from EMA and the trial registry clinicaltrials.gov. Reimbursement documents were retrieved from the websites of the assessing agencies.

Data extraction

Information on the name of the active substance, date of approval, initial indication, the clinical data of the pivotal studies, the risk-benefit assessment by the CHMP and additional requirements for the marketing authorisation holder was extracted from the EPAR. For the overview of the additional evidence information was extracted on the type of study, indication, number of patients and for two products also the main outcome. For the analysis of the reimbursement assessments, the main remarks on the effectiveness, safety, cost-effectiveness, budget impact, severity of disease and ease of use were extracted as well as the conditions to the reimbursement, including patient access schemes, and the final recommendation.

2 Background

This chapter gives an overview of all the relevant regulations and policies, additional information on reimbursement strategies, information on the selected reimbursement agencies and an introduction to the financing of oncology drugs.

2.1 EMA

2.1.1 Authorisation procedures for medicinal products in the European Union

The European system offers several routes for introducing a medicinal product to the European market.

The Centralised Procedure allows for authorisation of medicinal products to the entire market of the European Community through a single application and evaluation by the EMA [12]. Within the EMA, the CHMP is responsible for preparing the Agency's opinions on all questions concerning medicines for human use. The procedure is laid down in Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 [1].

The centralised procedure is mandatory for all medicinal products derived from biotechnology, designated orphan products and new actives substances intended for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, auto-immune diseases, immune dysfunctions and viral diseases. The procedure is optional for other new active substances and medicinal products that constitute a significant therapeutic, scientific or technical innovation. Generic applications for active substances that have already been authorised via the centralised procedure have automatic access to the centralised procedure.

After applicants have notified the EMA of their intention to submit an application, a Rapporteur and Co-Rapporteur are appointed from amongst the members of the CHMP. The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP. This assessment report receives comments from other CHMP members which are incorporated into the report and communicated to the applicant. After submitting the applicants' replies to the CHMP for discussion, the Rapporteur and Co-Rapporteur prepare a final assessment report. The CHMP then gives a favourable or unfavourable opinion as to whether to grant the authorisation. The time limit for this procedure is 210 days, with the possibility for the applicant to apply for an accelerated assessment of max 150 days, when it concerns a product of major public health interest. The decision is ultimately made by the European Commission. A European Public Assessment Report (EPAR) will be published when the Commission issues its decision. When the decision is negative, a "Refusal EPAR" is published.

**centralised Procedure
laid down in Regulation
(EC) No 726/2004**

**centralised procedure
is mandatory for orphan
drugs and innovative
oncologic drugs**

a normal marketing authorisation is valid for five years

Under normal circumstances, the marketing authorisation is valid for five years. After five years the CHMP re-evaluates the benefit-risk balance of the product. When the marketing authorisation gets renewed, it will be valid for an unlimited period, unless otherwise specified.

beside the centralised procedure there is the mutual recognition procedure and the decentralised procedure

There are other options for gaining marketing authorisation in the European Communion. The mutual recognition procedure is intended for products that have already got authorisation in one of the Member States, which will be recognised by other Member States. The decentralised procedure is like the mutual recognition procedure, also based on recognition by national authorities of a first assessment performed by one Member State. The difference is that it applies to medicinal products which have not received a marketing authorisation in any European member state at the time of application. Also national authorisations are still available for medicinal products to be marketed in one Member State only, when the centralised procedure is not mandatory.

2.1.2 Orphan Medicinal Product Designation

orphan drug regulation has been implemented in 2000 in Europe

Orphan drug regulation is not a European invention. The Orphan Drug Act (ODA) from 1983 is said to be one of the most successful United States legislative actions in recent history [13]. Similar regulations came into force in Singapore (1991), Japan (1993), Taiwan and Australia (1998) and lastly in the EU (2000) [14]. The European parliament and the Council of Europe have adopted the regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products, with the intention to stimulate research, development and bringing to the market of medications for rare conditions [1]. This regulation gives developers of medicinal products the opportunity to apply for orphan designation for their product, providing them with various advantages in the field of protocol assistance, access to the Centralised Procedure and marketing exclusivity.

a condition is 'orphan' when not more than 5 in 10,000 people in the EU are affected

In the EU, medicinal products are eligible for orphan designation if it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 people in the European Community at the time of the application or if it is unlikely that without incentives the marketing of the medicinal product would generate sufficient return to justify the necessary investment. Additionally there needs to be an absence of alternatives and if such an alternative does exist, the medicinal product needs to be of significant benefit to the people affected by the condition [1].

orphan designation is assigned by the Committee for Orphan Medicinal Products

An application for orphan designation can be submitted any time before the application for marketing authorisation is made. The Committee for Orphan Medicinal Products is responsible for examining the applications. Designated medicinal products are entered in the Community Register of Orphan Medicinal Products. The sponsor has to report to the EMA on the state of development of the product on a yearly basis. Designated products can be removed from the register for three reasons: 1) at request of the sponsor, 2) if it is established that the criteria for designation are no longer met or 3) at the end of the period of market exclusivity.

The developer of a designated product may request protocol assistance in the development of the product before marketing authorisation and can apply for various fee reductions on protocol assistance, pre-authorisation inspections, the initial application, post authorisation applications and the first annual fee. Most importantly however, the sponsor can get market exclusivity for 10 years, wherein no similar medicinal product for the same therapeutic indication shall be granted marketing authorisation. Exceptions can be made when either the holder of the original marketing authorisation has given his consent or is unable to supply the product in sufficient amounts or the second medicinal product is clinically superior. The market exclusivity can also be reduced to six years, if at the end of the fifth year is established that original designation criteria are no longer met.

the benefits for the developer are protocol assistance, fee reductions and 10 year market exclusivity

2.1.3 Applications in exceptional circumstances

The procedure for granting a marketing authorisation under exceptional circumstances is outlined in a guideline published by EMA [2]. A marketing authorisation may be granted under exceptional circumstances when an applicant for marketing authorisation is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because of one of the following reasons:

exceptional circumstances can be granted when the collection of comprehensive efficacy and safety data is impossible

- ✧ the indication is too rare;
- ✧ the present state of scientific knowledge needed to provide comprehensive information is insufficient;
- ✧ it would be unethical to collect such information.

Once exceptional circumstances are granted, the applicant may be subjected to specific obligations such as additional efficacy or safety studies, there may be restrictions on the setting in which the product is used (e.g. inpatient or outpatient) and there may be additional requirements to the package leaflet and medical information of the product.

the indication is too rare, the present state of scientific knowledge is insufficient or it would be unethical

Marketing authorisations under exceptional circumstances are reviewed on an annual basis to reassess the risk-benefit balance. The fulfilment of the specific obligations concerning the provision of additional efficacy or safety data will normally not lead to the completion of a full dossier and a normal marketing authorisation. If it is expected that the applicant can confirm the positive benefit/risk balance with a full dossier in the future, the product could be authorised under conditional approval. This temporary authorisation is also assessed annually and is not intended to remain conditional. Orphan designation criteria are independent from the criteria to be considered for approval under exceptional circumstances [2].

risk/benefit reviewed on a yearly basis

2.1.4 Conditional approval

conditional approval is possible when the risk-benefit balance is positive, but part of the clinical data is still awaited

Medicinal products are eligible for conditional approval by the EMA if they belong to *one* of the three following categories:

- ✦ medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
- ✦ medicinal products to be used in emergency situations, in response to public threats duly recognised either by the WHO or by the Community in the framework of Decision (EC) No 2119/98;
- ✦ medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

a high medical need must be met

Additionally they have to meet *all* of the following requirements:

- ✦ the risk-benefit balance of the medicinal product is positive;
- ✦ it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- ✦ unmet medical needs will be fulfilled;
- ✦ the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

valid for one year

Conditional marketing authorisations are valid for one year and can be renewed. As with exceptional circumstances, specific obligations may be imposed in relation to the collection of data. The main difference is that the authorisation is not intended to remain conditional.

introduced in 2006

Before conditional approval was introduced in 2006, authorisations that should have fallen into this category were authorised under exceptional circumstances. Therefore a lot of drugs that were initially authorised under exceptional circumstances now have a regular marketing authorisation [15].

2.2 Reimbursement aspects

2.2.1 Healthcare systems introduction

european countries mostly have a national health service or an insurance-based healthcare system

There is a variety in the way healthcare systems are organized in Europe. Most countries have either a national health service (England and Scotland) or an insurance-based healthcare system (Belgium, France and the Netherlands). The insurance-based systems can be either 'social' or 'private' [16].

insurance-based systems can be social or private and are funded by premiums

Social insurance-based healthcare systems rely on the principle of solidarity in population coverage, funding and benefits package. They have the important commonalities that the contributions are risk independent, i.e. they are not linked to health status, and they are transparently collected independent from state general revenues [17]. Private insurance-based healthcare systems, like in the United States of America, are not common in Europe. The ones that do exist work under social conditions, which means acceptance is mandatory (the Netherlands). However, in almost all European member states it is possible to buy additional private insurance [16].

A national health service is primarily funded through general taxation rather than requiring insurance payments. Table 2.2-1 lists an overview of the main characteristics of the countries included in the report.

a national health service is funded through general taxation

2.2.2 Reimbursement and financing aspects

Reimbursement of pharmaceuticals for outpatient use is often established in a positive list; a legally binding index of pharmaceuticals that are reimbursed by the national health service/health insurance system. A negative list is also a possibility, in which case certain pharmaceuticals are specifically excluded from reimbursement/funding. Belgium, France and the Netherlands work with a positive outpatient list. England and Scotland work with a negative list. For inpatient use, national lists of pharmaceuticals are less common, but Belgium and France have a positive list for inpatient pharmaceuticals. England and Scotland have a negative list for inpatient pharmaceuticals [16].

reimbursement of pharmaceuticals is generally established in positive or negative lists

Co-payments on pharmaceuticals are common in almost all healthcare systems, but differ in quantity and form. They can be found in the form of fixed-fees, prescription-fees, percentages of the price of the pharmaceutical or the difference between the list price and the retail price (see Table 2.2-1).

co-payments are common in most EU countries

Oncology drugs are dispensed and administered in both the inpatient and outpatient setting. Some of them are suitable for self-administration, mainly those that can be taken orally or certain injectable dosage forms, and they can be dispensed by community pharmacies. Other dosage forms, like intravenous infusions, are mainly administered in a clinical setting, often the hospital. The setting in which the drugs are used is in most countries of influence on the way they are financed.

oncologic drugs are used in both the inpatient and outpatient setting

Table 2.2-2 show an overview of the agencies and institutes involved in reimbursement assessments and decisions in the selected countries.

Belgium

The healthcare system in Belgium is a social insurance-based system and it's for the largest part funded from health insurance contributions, general taxation and co-payments. In Belgium, co-payments on outpatient pharmaceuticals are common, but on life-saving drugs there is no co-payment. For inpatient drugs patients pay € 0,62 per hospitalisation day [18].

in Belgium there is no co-payment on life-saving drugs, like oncologic drugs

Reimbursement assessments are performed by the National Institute for Sickness and Invalidity Insurance (RIZIV). They are initiated by an application from the manufacturer. The assessment is based on the therapeutic value, which includes effectiveness, safety, applicability and ease of use, price, medical need, budget impact and cost-effectiveness. On the basis of the advice from RIZIV, the Ministry of Social Affairs will make a reimbursement decision. Since Belgium works with a positive list for both in- and outpatient pharmaceuticals, only evaluated pharmaceuticals are eligible for reimbursement [16].

the reimbursement assessment in Belgium is performed by National Institute for Sickness and Invalidity Insurance

the national health services in England, Wales, Scotland and Northern Ireland are separately managed

in England the National Institute for Health and Clinical Excellence performs health technology assessments

NICE maintains a strict maximum ICER of £ 30,000 per QALY, but exceptions are made for life-extending, end of life treatments

reimbursement assessments in France are performed by the Transparency Committee of the Haute Autorité de Santé

England

The National Health Service in the United Kingdom is a publicly funded health system. Although it is funded from national taxation, the National Health Service (England), the Health and Social Care in Northern Ireland (HSENI), the NHS Scotland and the NHS Wales are managed separately. The NHS England is divided into 10 Strategic Health Authorities, which supervise all NHS trusts in their respective area. The primary care trusts are local organisations in charge of primary care and control 80 % of the NHS budget. They allocate the budgets to the hospitals [19].

The National Institute for Health and Clinical Excellence (NICE) was set up in 1999 to reduce variation in the availability and quality of NHS treatments and care. NICE develops evidence-based guidelines on diagnosing, treatment and prevention [20]. The Centre for Health Technology Evaluation (CHTE), within NICE, develops single technology appraisals, which are recommendations on the use of new and existing medicines and treatments within the NHS. The development of a single technology appraisal is quite an extensive process. The topics are referred to NICE by the Department of Health. Then evidence is gathered from both the manufacturer and independent consultees. The evidence is reviewed by an independent academic centre after which clinical experts, patients and carers can comment on it. The appraisal committee then produces its final appraisal determination with recommendations on how the technology should be used in the NHS in England and Wales. Within this process there are several moments for stakeholders, such as the manufacturer and patient representatives, to comment, discuss or appeal. Once finalised, the advice issued by NICE is binding for the primary care trusts and funding has to be available within three months [21].

NICE maintains a strict maximum ICER of £ 30,000 per QALY gained when recommending technologies, but has the option to make exemptions for life-extending, end of life treatments. The three main criteria that are to be satisfied are 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and; 2) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment and; 3) the treatment is licensed or otherwise indicated, for small patient populations [22].

France

After market authorisation of a pharmaceutical, the Transparency Committee of the Haute Autorité de Santé (HAS) evaluates the medical benefit (Service Médical Rendu, SMR) and the improvement in medical benefit (Amélioration du Service Médical Rendu, ASMR). The SMR is a three point scale ranging from SMR I; pharmaceutical of major therapeutic value to SMR III; pharmaceutical of insufficient therapeutic value and the ASMR is a six point scale ranging from ASMR I; significant therapeutic value to ASMR VI; negative opinion regarding inclusion into reimbursement. Subsequently the Transparency Committee advises on inclusion on one or both of the positive lists; the outpatient list (la liste des médicaments remboursable agréés aux assurés sociaux) and the inpatient list (la liste des médicaments agréés aux collectivités). The SMR determines the rate of reimbursement; 100 %, 65 % or 35 %. The reimbursement rate for cancer treatment is always 100 %. Inpatient pharmaceuticals are financed through a diagnosis related group-type system. Additionally there is the T2A-list of innovative and expensive pharmaceuticals, that are financed separately [23].

The Netherlands

The reimbursement evaluation of pharmaceuticals is generally initiated by an application by the marketing authorization holder to the minister of Health, Welfare and Sports (VWS). The minister is assisted in her decision by the Healthcare Insurance Board (CVZ). Within the CVZ, the Committee Pharmaceutical Aid (CFH) will draw up an ‘assessment of therapeutic value’ and make a budget impact estimate. For new chemical entities, the CFH will also give an opinion on the justification of the efficiency (cost-effectiveness). The therapeutic value of a pharmaceutical is based on five criteria: positive effects, negative effects, experience with the drug, applicability and ease of use. The weight of these criteria is carefully determined in each case. Costs play no role in the assessment of therapeutic value. Based on the report from the CFH, the appraisal committee gives its opinion on the four principles of the benefits of Dutch basic health insurance, necessity (disease burden), effectiveness, cost-effectiveness and practicability. Based on the CFH and the appraisal committee reports, the CVZ issues an advice to the minister, who makes the ultimate decision to designate a pharmaceutical for reimbursement by the insurance companies [24].

Inpatient pharmaceuticals are not reimbursed by the health insurers, but are paid from the hospital budget. To counteract the so-called ‘postcode prescribing’ (expensive pharmaceuticals only being available in certain regions or hospitals), two policies were introduced in 2006 to provide additional funding for really expensive innovative drugs (costs of at least 2,5 million Euros per drug per hospital per year) and orphan drugs (when the yearly costs of the drug exceed 5 % of the total drug budget). Applications for this funding cannot be made by the manufacturer, but have to be made by parties like the clinicians organizations. Additionally, the funding is always conditional. After four years, the drug is reassessed on budget-impact, therapeutic value and cost-effectiveness. A dossier for this assessment has to be submitted by the party that originally applied for the funding, but the necessary research is a joint responsibility of the manufacturer, clinicians and the healthcare institutes. As of 2012 these two policies are no longer active. Funding for these drugs is now included in the hospital budgets again. The evaluation process however, has not been changed [25-27].

Scotland

In Scotland the Scottish Medicines Consortium (SMC) evaluates all newly licenced pharmaceuticals on the basis of a dossier submitted by the manufacturer. If the manufacturer decides not to submit a dossier, the SMC will not recommend a drug. The assessment performed by the SMC is based on the effectiveness, safety, target population, costs and cost-effectiveness. If the SMC recommends a pharmaceutical, local NHS boards have to decide if they want to include it into their local formulary. The NHS Quality Improvement Scotland considers if the advice given by NICE is relevant to patients in Scotland. If so, they publish the advice on their websites and the local NHS boards have to consider it for their local formularies [28].

in the Netherlands reimbursement evaluations are performed by the Healthcare Insurance Board

inpatient pharmaceuticals are paid from the hospital budget but additional funding is available for orphan and very expensive drugs

in Scotland the Scottish Medicines Consortium evaluates all newly licenced drugs

Table 2.2-1: Main characteristics of the healthcare systems and reimbursement of pharmaceuticals of the countries included in the report

	Belgium	England	France	The Netherlands	Scotland
Type of healthcare system	Insurance-based	National health service	Insurance-based	Insurance-based	National health service
Health insurance is mandatory	Yes	NA	Yes	Yes	NA
Social insurance	Yes	No	Yes	No	No
Private insurance is the main type	No	No	No	Yes	No
Reimbursement list					
Type of list outpatient pharmaceuticals	Positive	Negative	Positive	Positive	Negative
Type of list inpatient pharmaceuticals	Positive	Negative	Positive	NA	Negative
Co-payments outpatient pharmaceuticals					
% of the price	X		X		
Fixed fee			X		
Payment of difference between reference price and retail price	X			X	
Prescription fee		X			
Deductible				X	
Annual co-payment ceiling	X				

Source: Kleijnen et al, 2011 [16]

Abbreviations: NA – Not applicable

Table 2.2-2: Agencies and organisations involved in reimbursement decisions in the countries included in the report

	Belgium	England	France	The Netherlands	Scotland
Reimbursement evaluations	Always, inpatient and outpatient	Always for branded, oncology an autoimmune disease, sometimes for generics and orphan	Always for branded, oncology, autoimmune and orphan, sometimes generics	Yes, not for generics, sometimes for inpatient use	Always for oncology, autoimmune and orphan, sometimes for branded, never for generics
Agency that performs the assessment	INAMI/RIZIV (Institut national d'assurance maladie-invalidité/ Rijksinstituut voor Ziekte – en Invaliditeits Verzekering)	Product sponsor/ academic group (rapid) academic group/ stakeholders (full)	Haute Autorité de Santé (HAS) (French National Authority for Health)	Health Care Insurance Board (CVZ)	Scottish Medicines Consortium (SMC)
Organisation that provides advice for the decision	INAMI/RIZIV	National Institute for Health and Clinical Excellence (NICE)	HAS	CVZ	SMC
Organisation that makes the decision	Ministry of Social Affairs	NICE/NHS primary care trust	Ministry of Health and Social Affairs	Ministry of Health, Welfare and Sport (VWS)	Regional Health Authority

Source: Kleijnen et al, 2011 [16]

2.2.3 Patient Access Schemes

Where reimbursement decisions traditionally only focused on whether to pay for a product, for the entire indication, or for a particular subgroup, recently a number of new ways to finance pharmaceuticals have been introduced, so called patient access schemes. These schemes can be classified in different ways which are discussed below [29, 30].

Coverage with evidence development

coverage with evidence development can be divided into ,only in research' and ,only with research'

Coverage with evidence development (CED) can be divided into 'only with research' where all patients are given access to the treatment, but evidence is also generated, an 'only in research' where the treatment is only paid for patients involved in the research. These types of schemes are particularly useful for treatments that appear promising, but may not yet have the required supporting evidence [29, 30]. The generating of additional evidence can take place in various settings. The marketing authorisation holder is not always the sole responsible party, but also patient organizations and scientific bodies can have interests in additional clinical evidence and proof of cost-effectiveness, as it can assist in more adequate use of resources. CED has been standard practice for expensive or orphan, inpatient pharmaceuticals in the Netherlands since 2006, with varying results.

Conditional treatment continuation

conditional treatment continuation is related to short-term target clinical effects

In conditional treatment continuation (CTC) a treatment will only continue to be reimbursed when a short-term target clinical effect is reached. These schemes require the existence of a short-term measure that is an acceptable surrogate for relevant clinical endpoints. CTC is particularly useful when doctors and patients are inclined to continue treatment merely because of a lack of alternatives [29]. An example of such a reimbursement scheme is the agreement between Johnson and Johnson and the UK's NHS. Bortezomib, used in the treatment of progressive multiple myeloma, is only continued in people who have a complete or partial response, measured by serum M protein, after a maximum of four cycles. Johnson and Johnson rebates the full cost of bortezomib for people who have less than a partial response [31].

Performance linked reimbursement

performance linked reimbursement is dependent on a certain treatment goal

When the generation of more evidence is very expensive, but the manufacturer has sufficient confidence in its product or when a therapy is clearly effective in certain patients, but cost-effectiveness criteria are not reached, a performance-linked reimbursement scheme can be appropriate. The majority of performance-linked reimbursement schemes involve rebates or refunds when a certain treatment goal is not reached [29]. A recent example of such a scheme is the pay-for-performance agreements of August 2012 between hospitals in the Netherlands and Novartis, for the drug omalizumab (Xolair), used in the treatment of severe asthma. Novartis has agreed to pay for the treatment of patients with omalizumab that turns out to be unsuccessful. The Dutch association of physicians for pulmonary disease is responsible for the inclusion and evaluation criteria of the patients and the hospital pharmacy is responsible for reclaiming the costs of omalizumab in case of an unsuccessful treatment. For the Netherlands, this is the first pay-for-performance reimbursement scheme and therefore it will initially last for two years [32].

Non-outcome-based schemes

Additional to these health-outcomes-based schemes, there are multiple non-outcome-based schemes, where effective prices can be determined on a patient or population level. An example of a patient level scheme is the discount on treatment initiation with sunitinib in renal cell carcinoma. The manufacturer of sunitinib (Pfizer) has agreed a patient access scheme with the Department of Health, in which the first treatment cycle of treatment is free to the NHS [33]. A fixed cost per patient is agreed between the manufacturer of gefitinib (Astra Zeneca) and the Department of Health. Gefitinib for first-line treatment of non-small cell lung cancer will be available at a single fixed cost of £ 12,200 per patient irrespective of the duration of treatment. On top of that the manufacturer will not invoice the NHS until the third monthly pack of gefitinib is supplied. This means that treatment that lasts less than 3 months will not be charged by the manufacturer [34]. Population level schemes include discounts for payers on the list price, total expenditure caps and price/volume agreements [30].

**non-health
outcome – based
schemes include
discounts, fixed costs
per patient and price/
volume agreements**

3 Results

3.1 Oncology drugs under exceptional circumstances

four oncologic drugs are currently licenced under exceptional circumstances

The search on the EMA website yielded that there are currently only four oncologic drugs authorised under exceptional circumstances; nelarabine, clofarabine, histamine dihydrochloride and trabectedin (Table 3.2-1). Seven other oncologic drugs have previously been authorised under exceptional circumstances, but later received a normal licence, with six being still on the market. (Alemtuzumab has been withdrawn for commercial reasons.)

3.2 Clofarabine – Evoltra

3.2.1 Indication

acute lymphoblastic leukaemia is a cancer of the blood and bone marrow

Acute lymphoblastic leukaemia (ALL) is a cancer of the blood and bone marrow, in which too many immature lymphocytes are produced. Blood stem cells produced in the bone marrow can develop in either a myeloid stem cell or a lymphoid stem cell. Myeloid stem cells can develop in three types of mature blood cells; red blood cells, blood platelets or granulocytes. Lymphoid stem cells develop via lymphoblasts into T-lymphocytes, B-lymphocytes or natural killer cells. In ALL too many lymphoblasts, T-lymphocytes or B-lymphocytes are produced. These immature cells are not only unable to fight infections properly, their large amounts are also displacing the healthy blood cells, which may lead to infection, anaemia and blood coagulation disorders [35].

prevalence estimated at 8.1/100,000

The overall incidence rate in Europe of leukaemia in children aged 0-14 years was 44 per million person-years during 1988-1997. Lymphoid leukaemia (LL), which mostly consists of ALL, accounts for around 81 % of leukaemia [36]. Orphanet estimates the prevalence of ALL on 8.1/100,000 [37].

important prognostic factors are leukocyte count, genetics of the leukaemia cells and patients PD/PK

There are multiple kinds of prognostic factors that can predict the outcome of treatment. Clinical features like age and leukocyte count at diagnosis are strong prognostic factors in patients with B-cell precursor ALL. Secondly, the genetics of the leukaemia cells play an important part in risk stratification. Thirdly, the patient's pharmacokinetics and pharmacodynamics are of influence on treatment response. Early response to treatment, influenced by all three features, is consequently the most powerful predictor of outcome. The measurement of minimal residual disease, which is the presence of leukaemic cells below the threshold of detection by conventional morphologic methods, with the use of either flow cytometry or polymerase-chain-reaction, can therefore be an important guide in post-induction treatment [38, 39].

Table 3.2-1: Oncology drugs authorised under exceptional circumstances by the EMA

International Nonproprietary Name	Brand Name	Authorisation date	Original licenced indication	Date of regular marketing authorisation
docetaxel	Taxotere	27.11.1995	Second line monotherapeutic treatment of patients with advanced breast cancer after anthracycline failure	07.07.1998
alemtuzumab	MabCampath	06.07.2001	Treatment of patients with B-cell chronic lymphocytic leukaemia (BCLL) for whom fludarabine combination chemotherapy is not appropriate.	04.07.2008
temoporfin	Foscan	24.10.2001	Palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy.	21.05.2008
imatinib	Glivec	07.11.2001	Adult patients with Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (CML) in chronic phase after failure of interferon- alpha therapy, or in accelerated phase or myeloid blast crisis	13.04.2007
arsenictrioxide	Trisenox	05.03.2002	Induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the pro-myelocytic leukaemia/retinoic-acid-receptor alpha (PML/RAR-alpha) gene. Previous treatments should have included a retinoid and chemotherapy.	10.08.2010
ibrutinomabtiuxetan	Zevalin	16.01.2004	Treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).	22.05.2008
bortezomib	Velcade	26.04.2004	Treatment of patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy	19.03.2012
clofarabine	Evoltra	29.05.2006	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.	–
nelarabine	Atriance	22.08.2007	Treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.	–
trabectedin	Yondelis	17.09.2007	Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.	–
histamine dihydrochloride	Ceplene	07.10.2008	Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.	–

Treatment

**treated with r
emission-induction
therapy followed by
intensification**

Treatment schedules in ALL are adapted to phenotype, genotype and risk of the disease subtype. Except for mature B-cell ALL, all subtypes are treated with both remission-induction therapy followed by intensification (or consolidation) therapy. Allogeneic hematopoietic stem-cell transplantation (HSCT) is not always indicated. Remission-induction therapy aims at reducing the amount of leukaemia cells to 1 % or less of the initial burden. It usually consist of three or four different drugs; vincristine, a corticosteroid, L-asparaginase and/or anthracycline [35, 38]. Remission-induction, when successful, is followed by treatment intensification. These treatment schedules can largely vary between studies and populations, but in childhood ALL high-dose methotrexate, cytarabine, mercaptopurine and high-dose asparaginase are commonly used. Maintenance treatment follows for another two to three years, consisting usually of weekly methotrexate and daily mercaptopurine, potentially supplemented with other agents.

To clear leukaemic cells from the central nervous system (CNS) and to prevent CNS-relapse, CNS-directed therapy is given to all patients with ALL. This can either exist of intrathecal therapy, CNS-penetrant chemotherapy or cranial radiation. CNS-treatment is also adapted to the risk profile of the patient [35, 38,39].

Relapse

**approximately 25-30 %
of children relapse or
are refractory to initial
therapy**

Complete remission (CR) is reached in >95 % in children and in 60-80 % in adults. Approximately 25-30 % of children relapse or are refractory to initial therapy. Relapse within 6 months results in a 10-20 % chance of long-term survival, whereas relapse over one year after completion of initial therapy results in a slightly better outlook with cure rates of 30-40 % [40, 41].

**for patients in second
relapse all established
treatment options would
have been exhausted**

Patients in second remission still have a poor outcome and are therefore recommended for an allogeneic bone marrow transplantation (BMT), stem cell transplantation (SCT) or autologous transplantation. For patients in second relapse, who would normally have received at least two multi-agent chemotherapy regimens, all established treatment options would have been exhausted [41].

3.2.2 Mechanism of action

**nucleoside analogue
anti-metabolite
anticancer agent**

Clofarabine is a nucleoside analogue anti-metabolite anticancer agent. Its cytotoxicity results from the inhibition of ribonucleotide reductase and DNA polymerase [42].

3.2.3 Summary of licensing documents

Clofarabine was approved by the EMA on 29 May 2006 for the treatment of paediatric patients with relapsed or refractory ALL after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.

Efficacy

The demonstration of efficacy was based on one pivotal phase II study (CLO-212) [41]. Due to the limited number of patients in second relapse, no extensive clinical development program was conducted. Study CLO-212 was an open label, non-randomised, single-arm study in paediatric patients with ALL in second or subsequent relapse and/or refractory, who were ≤ 21 years of age at time of initial diagnosis. The primary efficacy endpoint in this study was the number of patients to achieve disease remission, categorised into complete remission (CR) defined as bone marrow blast counts $\leq 5\%$, no evidence of disease and full recovery of peripheral blood counts. CRp was defined as complete response without full haematologic recovery and partial remission (PR) was defined as complete disappearance of circulating blasts and bone marrow blast counts $\leq 25\%$. Overall 61 patients, with a median age of 12 years (range 1-20 years) were included in the study. Eighteen out of the 61 patients (30%) achieved a CR, CRp or PR. Twelve of these 18 patients achieved a CR or CRp (20%). A total of 10 children underwent HSCT, including 8 out of the 18 patients who had achieved a response. None of the responsive patients had any clofarabine-related or clinically significant toxicity that would have prevented HSCT.

one pivotal phase II study in 61 paediatric patients

Median survival for all patients was 12.9 weeks and greater than one year for patients who had responded to treatment. Although historical data are difficult to interpret, the EPAR states that data from Dutch and German cancer registries indicate that patients with multiply relapsed ALL have an estimated median survival of 9-10 weeks without further intervention.

Safety

The safety data in the application to the EMA were based on 132 paediatric patients (1-21 yrs) with either ALL or acute myeloid leukaemia (AML) who took part in one of several phase I or phase II studies [41]. According to the EPAR, the interpretation of safety data in uncontrolled studies is difficult though, because most patients are heavily pre-treated and might already suffer from on-going toxicity. The most frequently reported drug-related adverse events were nausea (61%), vomiting (61%), febrile neutropenia (32%), headache (24%), pyrexia (21%), pruritus (21%) and dermatitis (20%). Serious adverse events related to treatment with clofarabine were reported in 58% of the patients, but only 2 patients discontinued treatment due to an adverse event. Four deaths during the trials were considered by the investigators to be related to clofarabine. During the clinical trials with clofarabine, six cases of systemic inflammatory response syndrome/capillary leak syndrome were reported. Other risks associated with clofarabine are hepatic and cardiac toxicity and potentially renal toxicity. Important missing information is the safety of use for more than 3 cycles.

safety data based on 132 patients

Risk/Benefit

**lack of RCT justified
by small size of the
population**

The scientific discussion of the EPAR states that although an application would normally require data generated by randomised, controlled trials, the lack of it was justified by the small size of the population of patients in second relapse. The facilitating of HSCT by a partial or complete remission was considered a meaningful, clinical effect that may have an impact on duration of survival. The uncertainties regarding the safety profile of clofarabine were considered justified in view of the small size of the population of patients, but additional pharmacovigilance activities were considered necessary.

Specific obligations to be fulfilled by the marketing authorisation holder

**specific obligations
related to safety
measures and
pharmacokinetic data**

Outside of the risk management plan submitted by the manufacturer, the CHMP required additional risk minimisation activities in the form of a user's information package, to inform prescribers on the safe use of the drug, and the setup and promotion of a voluntary adverse event reporting system [41]. During the 3rd annually reassessment, additional obligations have been added [43]. The manufacturer was requested to supply population pharmacokinetics data and data to support the recommendation of dose adjustments in patients with moderate renal impairments. In the monitoring of adverse effects, extra attention was to be given to the monitoring of veno-occlusive disease after HSCT.

3.2.4 Additional publications

**few reports of
single-agent use of
clofarabine**

Table 3.2-3 presents an overview of all published trials and case reports of single-agent clofarabine in patients with ALL. A search of the literature yielded just five additional publications outside those mentioned in the EPAR, two retrospective reports and three case reports. One publication reports of five patients in the United Kingdom having been treated with single agent clofarabine outside of clinical trials [44]. Two of these 5 patients achieved a CR. Single agent therapy was only given during the early study period however, patients received combination therapy later on. In a retrospective study by the Spanish PETHEMA group, 5 of 31 patients were treated with single agent clofarabine treatment, 1 achieved a CR [45].

**additional trial
performed by the
manufacture has not
been published**

During the application at the EMA, a second open-label phase II study of clofarabine in paediatric patients with refractory/relapsed ALL had already started in Europe [41]. The design of the study BIOV-111 was similar to the pivotal CLO-212 trial. BIOV-111 had been completed in 2007 and the results were presented to the EMA in 2008 and to the FDA in 2010, but have not been published. The BIOV-111 results are said to be consistent with the final results of CLO-212 [46, 47]. Of 65 paediatric patients included, 3 patients (4,6 %) achieved a CR, 12 patients (18,5 %) achieved a CRp and 1 patient (1,5 %) achieved a PR. Seven out of 71 treated patients went on to transplant.

Table 3.2-2: Publications on clinical trials and case reports of single-agent use of clofarabine in patients with ALL

Source	Study ID	Journal	Type of Study	No. of Patients (total/ALL)	Age	CR+CRi
Barba et al, 2012 [45]		American Journal of Hematology	Retrospective	31	16-72	1/5*
O'Connor et al, 2011 [44]		British Journal of Haematology	Retrospective	23/5	0-17	2/5*
McGregor et al, 2009 [48]		Am J Hematol	Case Report	3	19-49	2/3
Johnston et al, 2008 [49]		Pediatric Blood & Cancer	Case Report	1	10	0/1
Jeha et al, 2006 [50]#	CLO-212	J ClinOncol	Phase II, open-label	61	1-20	12/61 (20 %)
Choi et al, 2006 [51]		Yale J BiolMed	Case Report	1	35	1/1
Jeha et al, 2004 [52]#	ID99-383	Blood	Phase I, dose-finding	25/17	1-19	7/17 (41 %)
Kantarjian et al, 2003 [53]#	ID00-038	Blood	Phase II, open-label	62/12	19-82	2/12 (17 %)
Kantarjian et al, 2003 [54]#	DM93-036	J ClinOncol	Phase I, dose-finding	51/13	>18	2/13 (15 %)
Genzyme [46, 47]	BIOV-111	Unpublished	Phase II, open-label	65	<21	15/65 (23 %)

... Studies included in licencing application

* In both studies, only five patients received single agent treatment.

3.2.5 Summary of reimbursement documents

Clofarabine has been assessed by RIZIV, HAS, CVZ and SMC and received a positive recommendation by all four agencies (Table 3.2-3). NICE has not assessed clofarabine. The amount of detail in the assessments varies between agencies.

RIZIV (Belgium) presented a very brief summary of efficacy and safety results from the pivotal trial in their assessment of 1 July 2008 [55]. They acknowledged the absence of alternative treatment for this patient group and declared clofarabine eligible for reimbursement. They did however impose two additional restrictions; a maximum of three cycles are reimbursed per patient and refractory patients have to have tried at least three different regimens before starting clofarabine.

RIZIV imposes restrictions on reimbursement

The Transparency Committee of HAS (France) issued an opinion on clofarabine on 13 December 2006 [56] and based its assessment on data from studies ID00-038 and CLO-212. They concluded that clofarabine significantly improves the treatment of ALL in relapsed or refractory children (ASMR II), despite the methodological limitations of the pivotal study.

HAS recommends clofarabine for reimbursement

CVZ (the Netherlands) determined the therapeutic value of clofarabine as compared to best supportive care in a report published on 24 September 2007 [57]. They based the evaluation on the product information and scientific discussion from the EPAR and the published result from studies ID99-383 [52] and CLO-212 [50]. They concluded that the results of treatment with clofarabine, short-term remission in about 25 % of the patients with the

clofarabine is included in the Dutch orphan drug financing policy

possibility long term remission after HSCT, were considerably better than the results of best supportive care and therefore clofarabine was recommended within its registered indication. It was included in the orphan drug financing policy.

SMC restricts clofarabine to patients that are eligible for HSCT

SMC (Scotland) issued an advice on 8 December 2006 [58] and adopted the opinion of EMA that even though there were no randomised clinical trials, the effects of clofarabine in terms of remission and facilitating HSCT were considered clinically relevant. The economic analysis presented by the manufacturer however, showed that cost-effectiveness for clofarabine was highly dependent on patients receiving HSCT after treatment. The use of clofarabine is therefore restricted to patients in whom it is being used to bridge to HSC.

Table 3.2-3: Main remarks on different aspects from the reimbursement evaluations of clofarabine

	CVZ	HAS	RIZIV	SMC
Decision date	24.09.2007	13.12.2006	01.07.2008	08.12.2006
Effectiveness	considerable better than best supportive care	actual benefit is substantial	capable of inducing remission	remission and facilitating HSCT is clinically significant
Safety	often severe side-effects, sometimes life-threatening	tolerance data are limited	list of AEs in trials	important risks identified from EPAR
Cost-effectiveness	–	–	–	highly dependent on HSCT
Budget impact	€ 700,000 per year	–	€ 639,180 per year	£ 216,000 per year
Severity of disease	–	–	–	–
Ease of use	mentioned	–	mentioned	–
Recommended	yes	yes	yes	yes
Conditions	evidence development		max 3 cycles, refractory patients after 3 prior regimens	only as a bridge to HSCT

Abbreviations: CVZ – College voor Zorgverzekeringen, HAS – Haute Autorité de Santé, RIZIV – Rijks Instituut voor Ziekte- en Invaliditeits Verzekering, SMC – Scottish Medicines Consortium, AE – adverse event, HSCT – Hematopoietic stem cell transplant, EPAR – European public assessment report

3.3 Nelarabine – Atriance

3.3.1 Indication

lymphoblastic leukaemia is considered the lymphomatous variant of ALL

Lymphoblastic leukaemia (LBL) is considered the lymphomatous variant of ALL (see chapter Clofarabine). The abnormal lymphocytes are generally in the lymph nodes or thymus gland and the bone marrow is lesser involved (<25 % marrow blasts). LBL is a form of non-Hodgkin lymphoma, a large group of cancers of lymphocytes. Treatment strategies for T-ALL and T-LBL are often the same, with comparable results [35, 59].

3.3.2 Mechanism of action

Nelarabine is the water soluble prodrug of 9-beta-D-arabinofuranosyl guanine (ara-G), an antineoplastic agent that acts as DNA synthesis inhibitor. Ara-G is converted intracellularly to the active triphosphate ara-GTP, in both B-cells and T-cells. Due to a more rapid catabolism in B-cells, ara-G is selectively toxic to T-cells owing to a greater exposure to ara-GTP [60].

**antineoplastic agent
and DNA synthesis
inhibitor**

3.3.3 Summary of licensing documents

Nelarabine received its marketing authorisation under exceptional circumstances on 22 August 2007. It is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Efficacy

In the application to EMA, the applicant presented two pivotal phase II open-label studies, one in patients ≥ 16 years of age (Study ID PGAA2002) and one in patients ≤ 21 years of age (Study ID PGAA2001) [61].

**two pivotal
phase II studies**

Study PGAA2001 was a phase II, open-label, multicentre clinical trial which included paediatric patient ≤ 21 years of age at diagnosis with refractory or recurrent T-ALL or T-LBL. Nelarabine was administered at a dose ranging from 400 mg/m² to 1200 mg/m² as a one-hour infusion daily over five days, every three weeks. The objectives of the study were to evaluate the response rate i.e. complete response (CR) defined as bone marrow blast counts $\leq 5\%$, no evidence of disease and full recovery of peripheral blood counts. CR* was defined as complete response without full haematologic recovery. Partial response (PR) was defined as bone marrow blast $\leq 25\%$. Secondary outcome measures included duration of response and overall survival. Five out of 39 patients in second relapse achieved a CR and an additional four patients achieved a CR*. The median duration of response was 12,3 weeks. Four of the nine patients in CR or CR* received an SCT. The median overall survival in patients in second relapse was thirteen weeks and the one-year survival was 14 %.

**one trial in adult
patients and one trial
in paediatric patients**

Study PGAA2002 was a similar study in adult patients ≥ 16 years of age with relapsed or refractory T-ALL or T-LBL. Nelarabine was administered at a dosage of 1500 mg/m² i.v. over 2 hours on days 1, 3, and 5 of a 21 day cycle. Objectives and outcomes were similar to study PGAA2001. Five out of 28 patients with two or more prior inductions achieved a CR and one additional patient received a CR*. The duration of response in patients in second relapse ranged from four to 195,4+ weeks. The median overall survival was 20,6 weeks and the one-year survival 29 %.

Safety

The safety evaluation in the EPAR was based on 459 adult and paediatric patients enrolled in four phase I studies and three phase II studies. Neurological toxicity was the dose-limiting toxicity and despite of an extensive phase I programme, early in the pivotal phase II trials additional dose-adjustments had to be made. In adult patients receiving the adjusted 1500 mg/m²

**safety data based
on 459 patients**

dose, the safety profile in terms of haematological and gastrointestinal effects was comparable to other cytotoxic agents. Neurological adverse events were reported in 8 % of the adult patients involved in phase II studies compared with 20 % in paediatric patients that received 650 mg/m². Ninety-nine per cent of the paediatric patients in this dose group experienced haematological toxicities. Among all the patients in the database, 13 % experienced a grade 3 neurological adverse event and 7 % a grade 4 neurological adverse event. The limited safety database resulted in specific post-marketing obligations.

Risk/Benefit

lack of RCT justified by small size of the population

The EPAR states that although normally an application would require data generated by randomised, controlled trials, the lack of it was justified by the small size of the population of patients in second relapse. And even though it was not possible to compare the response rate with anything, the magnitude was deemed clinically relevant because some patients were able to undergo a stem cell transplant. The uncertainties regarding the safety profile of nelarabine were considered justified in view of the small size of the population of patients, but additional pharmacovigilance activities were necessary.

Specific obligations to be fulfilled by the marketing authorisation holder

specific obligations related to safety measures

The CHMP required the following specific obligations:

- ✧ To provide data from an on-going phase III Children's Oncology Group study AALL0434, entitled "intensified methotrexate, nelarabine and augmented Berlin-Frankfurt-Münster therapy for children and young adults with newly diagnosed T-cell acute lymphoblastic leukaemia".
- ✧ To perform a post-marketing surveillance study for nelarabine in the indicated patient population under 21 years of age receiving the 650 mg/m² dose [62].

3.3.4 Additional publications

two additional clinical trials published

Table 3.3-1 presents an overview of all published trials and case reports of single-agent nelarabine in patients with ALL. A search of the literature yielded just six additional publications outside those mentioned in the EPAR, two clinical trials and four case reports. Two of the publications were in Japanese and could not be understood.

The single arm trial by Gökbuget et al [63] included thirteen patients in second relapse and reported a response rate of six complete remissions with or without full haematologic recovery. One-year survival however, was only 9 %. Information from clinicaltrials.gov indicates that nelarabine is currently being tested in several multi-agent regimens, in different clinical trials.

Table 3.3-1: Publications on clinical trials and case reports of single-agent use of nelarabine in patients with ALL

Source	Study ID	Journal	Type of Study	No. of Patients	Age median (range)	CR+Cri [95 %CI]
Gökbüget et al, 2011 [63]		J Clin Oncol	Phase II, single arm	Total=126 2 nd relapse=13	33 (18-81)	CR 6/13 (46 %)
Horibe et al, 2011 [64]	PGA105446	Rinsho Ketsueki	Phase I			
Papayannidis et al, 2010 [65]		Am J Hematol	Case report	1	30	CR, complete paraplegia
Iino et al, 2009 [66]		Rinsho Ketsueki	Case report			
Sigalas et al, 2009 [67]		Leuk Res	Case report	1	31	CR
Alvarado et al, 2007 [68]		Leuk Res	Case report	1	48	CR
DeAngelo et al, 2007 [69]#	PGAA2002	Blood	Phase II, single arm	Total=39, 2 nd relapse=28	34 (16-66)	29 % [13 %, 49 %]
Berg et al, 2005 [70]#	PGAA2001	J Clin Oncol	Phase II, single arm	Total=153, 2 nd relapse=39*	10.8 (2.5-20)	23 % [11 %, 39 %]
Kurtzberg et al, 2005 [71]#	PGAA1001	J Clin Oncol	Phase I, dose finding	Total=93, T-ALL/LBL=39	(3-75)	CR 9/39 (23 %)

... Studies included in licencing application

3.3.5 Summary of reimbursement documents

Nelarabine has been assessed by HAS, RIZIV and SMC and all three have recommended nelarabine for reimbursement (Table 3.3-2).

In the decision document from 1 June 2008 [72], RIZIV presented a brief overview of the results from the pivotal study, the incidence of ALL/LBL in Belgium and an estimation of the budget impact. In their re-evaluation in November 2010, it became clear that there was hardly any new information available. To that date, only one patient per year had been treated with nelarabine in Belgium.

RIZIV recommends nelarabine

The Transparency Committee of HAS issued an opinion on nelarabine on 19 December 2007 [73]. In their report they present a brief overview of the clinical efficacy and safety data from the two pivotal trials. They considered the efficacy/safety ratio of this product to be high and recognised the lack of alternative treatments in adult patients. Nelarabine was considered to provide a significant improvement in actual benefit (ASMR II), by facilitating access to an allograft in some patients. Therefore, nelarabine was recommended for reimbursement.

HAS emphasises the significant improvement in actual benefit

In their recommendation of 7 March 2008 SMC adopted the opinion of the EMA that the lack of randomised trials was justified in view of the small size of the population of patients in second relapse [74]. Additionally they accepted the complete response rate as a reasonable surrogate for clinical benefit. They deemed the economic analysis provided by the manufacturer to be of good quality, but cost-effectiveness was highly depending on HSCT and the assumed prolonged survival after that procedure. Therefore the SMC accepted the use of nelarabine only as a treatment to bridge to HSCT and not for palliation.

SMC restricts nelarabine to patients that are eligible for HSCT

nelarabine was not evaluated by NICE and CVZ

Nelarabine was not evaluated by NICE. It was considered for a potential technology appraisal, but rejected in July 2007 [75]. CVZ also did not evaluate nelarabine, because it was expected that the costs would not reach the threshold for additional funding.

Table 3.3-2: Main remarks on different aspects from the reimbursement evaluations of nelarabine

	HAS	RIZIV	SMC
Date	19.12.2007	01.06.2008	07.03.2008
Effectiveness	significant improvement in actual benefit	presented main efficacy results	meaningful response rates
Safety	few safety data	presented main AEs	presented main AEs
Cost-effectiveness	–	–	highly dependent on HSCT
Budget impact	–	max. € 510,134 per year	less than £ 107,000 per year
Severity of disease	–	–	–
Ease of use	–	–	–
Recommended	yes	yes	yes
Conditions			only to as a bridge to HSCT

Abbreviations: HAS – Haute Autorité de Santé, RIZIV – Rijksinstituut voor Ziekte- en Invaliditeitsverzekering, SMC – Scottish Medicines Consortium, AE – adverse event, HSCT – Hematopoietic stem cell transplant

3.4 Trabectedin – Yondelis

3.4.1 Indication

STS is a cancer that begins in the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body

prevalance is estimated at 23.7/100,000

Soft tissue sarcoma (STS) is a cancer that begins in the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body [76]. The World Health Organization has defined more than 50 histological subtypes [77]. The prevalence of STS in Europe is estimated at 23.7/100,000 [37]. STS is diagnosed by means of a biopsy for microscopic examination to determine the histologic type and tumour grade. Morphologic diagnosis is often complemented by ancillary techniques like immunohistochemistry, classical cytogenetics, electron microscopy and molecular genetic testing [78]. Prognostic factors in STS are the patient's age and the size, histologic grade, mitotic activity, and stage of the tumour [76].

Treatment

Treatment can consist of surgery, radiotherapy and chemotherapy

Factors of influence on STS treatment are the site of the tumour (e.g. head and neck, trunk, extremities) and stage of the tumour, for which multiple systems are used. The main treatment for localised disease is surgery. Surgical margins in STS are classified as intralaesional, marginal, wide and radical. Radiotherapy is applied in intermediate or high grade STS, large deep low grade sarcomas and incompletely resected tumours that are close to important structures [77]. Radiation therapy can be administered as primary therapy, preoperatively or postoperatively [78]. Chemotherapy is used in high grade tumours to shrink the tumour before surgery. Postoperatively it can increase relapse-free-survival. For advanced, unresectable or metastatic disease several regimens are available [78].

3.4.2 Mechanism of action

Trabectedin was initially obtained by isolation from the marine tunicate *Ecteiniascidia turbinata*, nowadays it is produced synthetically. Trabectedin predominantly binds to the minor groove of DNA and thereby delaying S-phase progression and inducing G2/M arrest. The precise mechanism of action however, is not completely understood [79].

precise mechanism is not completely understood

3.4.3 Summary of licensing documents

Trabectedin was authorised by the EMA on 17 September 2007, for the treatment of patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. An application for Marketing Authorisation submitted in November 2001 had previously been rejected [80].

Efficacy

In the first application, four phase I studies in patients with solid tumours were provided. In the second application an additional phase I study and a randomised, multi-centre, open-label study of trabectedin administered in two different schedules in patients with metastatic liposarcoma or leiomyosarcoma following treatment with an anthracycline and ifosfamide (ET743-ST5-201) were submitted.

This pivotal study ET743-ST5-201 was originally designed to select the most appropriate dosing schedule for further testing. After preliminary descriptive data suggested that one of the two treatment schedules would be more efficacious, the study was extended and the protocol amended, to allow for a direct comparison between treatment schedules. Information on the inclusion criteria and the intervention is missing from the EPAR but can be found in the article by Demetri et al, 2009 [81]. After the protocol amendment, patients were randomly assigned to one of two treatment schedules; trabectedin 1,5mg/m² in a 24-h infusion once every three weeks (q3wk 24-h) or trabectedin 0,58mg/m² in a 3-h infusion weekly every three out of four weeks (qw3 3-h). Crossover to the alternative treatment schedule was allowed after progressive disease. After the protocol amendment, the primary endpoint was changed to time to progression (TTP), calculated as the time between date of randomisation and date of disease progression. Secondary endpoints were overall objective response, progression-free survival and overall survival. Eligibility criteria included ≥18 years of age, histological confirmation of liposarcoma or leiomyosarcoma, unresectable and/or metastatic disease and prior treatment with at least an anthracycline and ifosfamide (combined or sequential). Tumours were assessed every eight weeks by a blinded independent review of diagnostic imaging by two radiologists, with a third radiologist resolving discrepancies [81].

on pivotal, double arm, uncontrolled, phase II study, 266 patients

At the time of the application to EMA, 266 patients had been randomly assigned to a treatment arm and were included in the primary analysis. The two study groups were well balanced for both demographic characteristic as well as prognostic variables. Time to progression at the primary analysis was 2.1 months (95 %CI 1.9-3.6) for the qw3 3-h treatment arm and 3.8 months (95 % CI 2.1-5.4) for the q3wk 24-h treatment arm. Although not statistically

significant, consistent trends were seen for PFS and OS. An updated report including new statistical analyses showed statistically significant results on the primary endpoint TTP. An additional survival analysis was requested by the CHMP. No statistically significant difference in survival was shown, but this might be due to crossover between treatment arms.

Table 3.4-1: Main outcomes of study ET743-STS-201

Primary analysis	q3wk 24-h	qwk 3-h
	n=132	n=134
TTP, median months [95 %CI]	3.8 [2.1-5.4]	2.1 [1.9-3.6]
PFS, median months [95 %CI]	3.5 [2.0-4.5]	2.1 [1.9-3.4]
OS, median months [95 %CI]	16.7 [12.2-n.r.]	11.8 [8.9-14.9]
Ancillary analysis	q3wk 24-h	qwk 3-h
	n=136	n=134
TTP, median months [95 %CI]	3.7 [2.1-5.4]	2.3 [2.0-3.5]

TTP – Time to progression, PFS – Progression free survival, OS – overall survival

Safety

safety data based
on 569 patients

After the last update, the assessment of safety was based on data from clinical trials in 569 patients treated with the recommended regimen in several cancer types. Approximately 91 % of the patients experienced any type of adverse event and around 40 % experienced a grade 3 or 4 adverse event. Most common adverse reactions were nausea, fatigue, vomiting, anorexia, neutropenia and increases in AST/ALT. Fatal adverse reactions have occurred in 1,9 %. Cumulative toxicity has not been observed [80].

Risk/Benefit

STS subtypes too rare
for a RCT

The EPAR states that trabectedin should ideally have been compared in an adequately designed and analysed randomised trial to best care or investigator's choice. This was not possible due to the absence of a control arm in the pivotal study. The applicant claimed that a comparison to best supportive care is considered very difficult in this patient population. The population of STS patients was considered heterogeneous and individual subpopulations are considered too rare for adequately powered randomised controlled trials to be conducted against best supportive care to explore factors associated with response to treatment within reasonable time. Conclusively, due to the rarity of the disease, the CHMP decided by consensus that the risk/benefit ratio of trabectedin was favourable and that the marketing authorisation could be granted under exceptional circumstances. Routine pharmacovigilance was considered adequate to monitor the safety of the product.

Specific obligations to be fulfilled by the marketing authorisation holder

specific obligations
related to predictors
of response

Because the authorisation was an approval under exceptional circumstances, the marketing authorisation holder had to conduct a further investigation in order to elucidate whether predictors of response to trabectedin in patients with STS could be identified. The final study report should have been submitted by 30 June 2012 [82]. This report is still awaited [83].

3.4.4 Additional publications

A search after additional published material of single-agent use of trabectedin in STS resulted in 25 articles of phase II clinical trials, retrospective case series analyses and case reports (Table 3.4-2). The retrospective case series analyses mostly included patients in compassionate use programmes.

**trabectedin
has been tested in
many STS subtypes**

Table 3.4-2: Publications of single-agent use of trabectedin in patients with soft tissue sarcoma

Source	Journal	Type of Study	No. ofPts	Subtype
Paz-Ares et al, 2012 [84]	Invest New Drugs	Phase II, uncontrolled	41	advanced or metastatic STS
Gronchi et al, 2012 [85]	Ann Oncol	Phase II, uncontrolled	29	myxoid liposarcoma, non-metastatic
Baruchel et al, 2012 [86]	Eur J Cancer	Phase II, uncontrolled	50	relapsed pediatric sarcomas
Monk et al, 2012 [87]	Gynecol Oncol	Phase II, uncontrolled	20	uterine leiomyosarcoma
Schöffski et al, 2012 [88]	Onkologie	Phase II, uncontrolled	28	STS
Sanfilippo et al, 2011[89]	Gynecol Oncol	Retrospective case series analysis	66	metastatic uterine leiomyosarcoma
Corrado et al, 2011 [90]	Gynecol Oncol	Case report	1	advanced uterine leiomyosarcoma
Schmitt et al, 2010 [91]	Mar Drugs	Retrospective case series analysis	25	STS excluded Ewing's and osteosarcoma
Fayette et al, 2010 [92]	Anticancer Drugs	Retrospective case series analysis	92	STS
Demetri et al, 2009 [81]	J Clin Oncol	Phase II, secondline	270	advanced or metastatic liposarcoma or leiomyosarcoma
Grosso et al, 2009 [93]	Ann Oncol	Retrospective case series analysis	32	myxoid liposarcoma
Amant et al, 2009 [94]	Int J Gynecol Cancer	Case report	5	uterine leiomyosarcoma
Roynance et al, 2007 [95]	Clin Oncol (R Coll Radiol)	Observational study	21	pre-treated advanced sarcoma
Grosso et al, 2007 [96]	Lancet Oncol	Retrospective case series analysis	51	myxoid liposarcoma
Tewari et al, 2006 [97]	Gynecol Oncol	Case report	1	metastatic uterine leiomyosarcoma
Garcia-Carbonero et al, 2005 [98]	J Clin Oncol	Phase II, first line	36	advanced STS
Therasse et al, 2005 [99]	Eur J Cancer	Phase II, non-randomised	49	advanced STS
Le Cesne et al, 2005 [100]	J Clin Oncol	Phase II, non-randomised	104	advanced STS
Blay et al, 2004[101]	Eur J Cancer	Phase II, non-randomised	28	advanced GIST
Garcia-Carbonero et al, 2004 [102]	J Clin Oncol	Phase II, non-randomised	36	advanced STS
Yovine et al, 2004 [103]	J Clin Oncol	Phase II, non-randomised	54	advanced STS
Laverdiere et al, 2003 [104]	Cancer	Phase II, non-randomised	25	osteosarcoma

Source	Journal	Type of Study	No. of Pts	Subtype
Demetri et al, 2002 [105]	Anticancer Drugs	Phase II, non-randomised	72	metastatic or advanced STS
Brain et al, 2002 [106]	Anticancer Drugs	Phase II, non-randomised	54	advanced pretreated STS
Delaloge et al, 2001 [107]	J Clin Oncol	Retrospective	29	sarcoma

3.4.5 Summary of reimbursement documents

Trabectedin was evaluated by all five agencies. The SMC was the only agency that did not recommend trabectedin (Table 3.4-3).

RIZIV recommends trabectedin

In the decision document from 13 November 2008, RIZIV presents a brief overview of the results from the pivotal study, contra-indications and ease of use, the incidence of STS in Belgium and an estimation of the budget impact. Because trabectedin has orphan status, an economic evaluation is not necessary.

NICE published extensive guidance, trabectedin is recommended with a patient access scheme

The NICE Guidance for trabectedin in the treatment of STS was published on 1 February 2010. Trabectedin was recommended with a patient access scheme, in which it is agreed that the acquisition costs of trabectedin for treatment needed after the fifth cycle are met by the manufacturer.

The clinical evidence submitted by the manufacturer included the pivotal trial and three additional uncontrolled phase II trials. As there were no controlled studies, historical control data from studies in the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) database were used to approximate best supportive care (BSC). The Committee concluded this to be appropriate for this disease area. They noted that the median overall survival and progression free survival for patients on the licenced dosage of trabectedin, exceeded that for patients receiving BSC, therefore they concluded that trabectedin was a clinically effective treatment.

a cost of £ 34,500 per QALY is accepted

In the guidance a lot of attention is given to the determination of the ICER, which is eventually estimated at £ 34,500 per QALY gained, with inclusion of the patient access scheme.

HAS recommends trabectedin

HAS published a report on trabectedin on 02 April 2008 and based their assessment on the pivotal study from the EPAR. Due to the lack of data from studies versus “supportive care” or a formalised comparison with a historic cohort, they concluded that trabectedin offers no improvement in actual benefit (level V). They do however recommend it for inclusion on the list of medicines approved for use by hospitals and various public services.

CVZ recommends trabectedin only for inpatient use

After an application by the manufacturer for reimbursement, CVZ issued a report on 28 April 2008 which did not recommend trabectedin for outpatient use [108]. It concluded that trabectedin as a second line therapy in leiomyo- and myxoid liposarcoma appeared efficacious, but that the sometimes severe, acute and deadly adverse effects make it unsuitable for outpatient use. In October 2009 the Dutch Federation for University Medical Centres applied for inclusion in the Orphan Drug policy, which was followed by a positive recommendation by CVZ on 22 February 2010 [109]. In this assessment, besides the EPAR, four additional studies were included (Yovine et al, Garcia-

Carbonero et al, 2004, Le Cesne et al, Roylance et al, Table 3.4-2). Due to the lack of randomised, controlled trials, they conclude that trabectedin appears to be efficacious and that it may be possible to increase the period of stable disease. An increase in overall survival has however not been proven. As required by the Orphan Drug policy, additional cost-effectiveness research is now being performed [110].

The evaluation by SMC from 11 August 2008 emphasised the limited efficacy data. The lack of comparisons with best supportive care or other therapy made it difficult to evaluate the additional clinical benefit. The cost-effectiveness evaluation submitted by the manufacturer was deemed unreliable. Where the manufacturer estimated the ICER to be £ 29,954 per QALY, the SMC had great doubts about the quality of the economic analysis and estimates the ICER to be at least £ 40,000. As a result, trabectedin is not recommended [111].

SMC does not recommend trabectedin on the basis of cost-effectiveness

Table 3.4-3: Main remarks on different aspects from the reimbursement evaluations of trabectedin

	CVZ	HAS	NICE	RIZIV	SMC
Date	22.02.2010	02.04.2008	01.02.2010	01.02.2009	11.01.2008
Effectiveness	appears to be effective	activity is minor and difficult to evaluate	clinically effective	presented main efficacy results	difficult to evaluate additional clinical benefit over standard practice
Safety	sometimes severe and fatal	mainly haematological and hepatic toxicity	most AEs reversible and non-cumulative	presented main AEs	presented main AEs and comments from EPAR
Cost-effectiveness			£ 34,500 per QALY		around £ 40,000 or higher
Budget impact	€ 5.3 million per year			€ 242.798 à € 353.161 per year	£ 243,000 in year 1 rising to £ 289,000 by year 5
Ease of use	IV infusion			central venous catheter	
Recommended	Yes	Yes	Yes*	Yes	No

* With patient access scheme

Abbreviations: CVZ – College voor Zorgverzekeringen, HAS – Haute Autorité de Santé, NICE – National Institute for Health and Clinical Excellence, RIZIV – Rijks Instituut voor Ziekte- en InvaliditeitsVerzekering, SMC – Scottish Medicines Consortium, AE – adverse event, EPAR – European public assessment report, QALY – Quality adjusted life-year

3.5 Ceplene – histamine dihydrochloride

3.5.1 Indication

AML is a cancer of blood or bone marrow cells from the myeloid lineage

Acute myeloid leukaemia (AML) is a cancer of blood or bone marrow cells from the myeloid lineage (See chapter clofarabine). In 2008 the AML-subtypes were reclassified under WHO supervision and now incorporate and interrelate morphology, cytogenetics, molecular genetics, and immunologic markers [112]. The older French-American-British (FAB) criteria relied solely on morphologic features [113]. Like in ALL, the leukaemia cells displace the healthy blood cells, which may lead to infection, anaemia and blood coagulation disorders. The estimated prevalence of AML in Europe is 16/100,000 [37].

leukaemia cell characteristics are an important prognostic factor

Prognostic factors in AML can be divided into patient characteristics, like age and general health condition, and leukaemia cell characteristics, like the karyotype of the cells and the molecular genetics. The monitoring of minimal residual disease is also in AML a tool to improve risk stratification [112].

Treatment

treatment consists of remission induction and post remission therapy.

Treatment strategies in AML differ from ALL strategies. AML treatment similarly starts with remission induction and is followed by postremission therapy. CNS prophylactic therapy and maintenance treatment however, are usually not indicated [112, 114]. The current standard for remission induction therapy is three days of an anthracycline (daunorubicin or idarubicin) or mitoxantrone, followed by seven days of cytarabine. CR is achieved in 60 % to 80 % of younger adults. There are multiple possibilities in postremission therapy, and in certain subtypes of AML some strategies have proven to be superior to others. High-dose cytarabine has improved outcome in patients with certain cytogenetic abnormalities. Autologous HSCT is an alternative for post-remission therapy in patients with favourable or intermediate risk cytogenetics. Allogeneic HSCT is associated with the lowest risk of relapse. This is attributed to both the high-dose regimen of the conditioning treatment and the graft-versus-leukaemia effect. Treatment related mortality limits the benefits unfortunately; therefore the risks associated with the transplant itself, e.g. comorbidities, should be an important factor in clinical decision making [112].

CNS prophylactic therapy and maintenance treatment are usually not indicated

3.5.2 Mechanism of action

histamine dihydrochloride is used together with interleukin-2

Histamine dihydrochloride (HDC) is a synthetic immune modulator, indicated for maintenance therapy for adult patients with AML in first remission concomitantly treated with interleukin-2 (IL-2). IL-2 is deployed to activate natural killer cells and T-lymphocytes that kill tumour cells. IL-2 has been administered to patients to prevent relapse in several randomised and non-randomised trials, but the result were inconsistent and failed to demonstrate a reduced frequency of relapse. The addition of HDC to improve the function of cytotoxic lymphocytes was based on in vitro and in vivo studies in multiple human malignant target cells and a phase II pilot study suggested it to be safe and feasible [115].

3.5.3 Summary of licensing documents

The application for marketing authorisation for Ceplene was submitted on 06 October 2006. After an initial refusal and re-examination by the EMA it was approved on 07 October 2008 as maintenance therapy indicated for adult patients with acute myeloid leukaemia in first remission, concomitantly treated with IL-2 [116].

Efficacy

The pivotal trial, study MP-MA-0201, was a randomised, open label, multi-center phase III trial with the main goal to compare the effect of HDC/IL-2 therapy versus no treatment on leukaemia free survival (LFS) in patients with acute myeloid leukaemia in complete remission. Three hundred twenty patients were included in the study and randomisation was stratified based on first or subsequent remission. The study showed a statistically significant difference in LFS in the population in first remission. Kaplan-Meier estimates of 3-year LFS were 26 % in the control group and 40 % in the HDC/IL-2 group ($p=0,02$). No significant differences were observed in the population in subsequent remission or in overall survival, but it should be noted that the study was not sufficiently powered for the latter [115, 116].

**pivotal, controlled,
phase III trial**

Safety

A total of 1,188 patients were treated with HDC and 689 control patients were part of the clinical development program. The most common adverse effects were flushing, hypotension, headache and injection site reactions. No study medication related deaths were reported. Quality-of-life levels were similar in both treatment groups [116].

**safety data based on
1,188 patients**

Risk/Benefit

After an oral explanation by the applicant to the CHMP, to address the outstanding issues, the CHMP decided that the risk-benefit balance for Ceplene was unfavourable. The main reason for this decision was the dependence on one pivotal study [116]. In document CPMP/EWP/2330/99 the EMA states that there is no formal requirement to include two or more pivotal studies, but in the exceptional event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency [117]. In the case of Ceplene, the CHMP considered the requirements of statistically compelling results not to be fulfilled. There was also only one supportive clinical phase II study available in only 39 patients. Thirdly, the pharmacological rationale was deemed to be weak and the supporting non-clinical data were not considered to be sufficient [116].

**initially the CHMP
decided against
authorisation**

After the initial recommendation, the applicant provided detailed grounds for re-examination including the opinion of expert European biostatisticians to support the pivotal trial and a review of the pharmacological rationale. For the re-examination of Ceplene, the CHMP consulted a scientific advisory group (SAG) in oncology to obtain advice on different matters relating to the clinical efficacy. There were different views on the robustness of the efficacy data and the support of the pharmacological rationale within the SAG. Some considered the single pivotal trial not to provide conclusive evidence due to marked heterogeneity between participating countries/centres, insufficient

**a re-examination
was performed and
a scientific advisory
group was consulted**

support of pharmacological rationale, non-clinical data provided, absence of proof of concept in eradication minimal residual disease and finally the negative outcome of the clinical trials with HDC/IL-2 in other indications. Others considered the biological rationale to be sound and found the uncertainty of the individual effects of the combination less important and considered the combination showed efficacy for a clinically relevant endpoint in a condition where there is a high medical need. Combined with the manageable toxicity, the benefits were considered important, even in the absence of extensive supportive data [116].

HDC was approved by majority decision

After reconsideration the CHMP concluded that the pivotal study could be considered as exceptionally compelling, particularly due to the high quality of the conduct of the study, the clinically and statistically significant results, and the internal validity. Also, the pharmacological rationale was accepted. HDC was approved by majority decision. Further clinical data were however requested [116].

Specific obligations to be fulfilled by the marketing authorisation holder

specific obligations concerned two additional trials

The marketing authorisation holder has to complete two post-authorisation obligations.

- ✧ A clinical study to evaluate the biomarkers and pharmacologic endpoints of Ceplene plus low dose interleukin-2 in approximately 100 adult patients stratified by age greater or less than 60 years with acute myeloid leukemia in first complete remission (CR), with well characterized morphologic, cytogenetic and molecular profiles, to be completed in the second quarter of 2013.
- ✧ A clinical study to evaluate minimal residual disease for the assessment of the anti-leukaemic activity of Ceplene plus low dose interleukin-2 in approximately 150 adult patients stratified by age greater or less than 60 years with acute myeloid leukemia in first complete remission, to be completed in the second quarter of 2013 [118].

3.5.4 Additional publications

there are no additional publication for HDC in AML

Since the marketing authorisation in October 2008, only one additional clinical study has been performed. According to the information from clinicaltrials.gov, the final data collection for the primary outcome measures should have been completed in August 2012. There are no additional publications for HDC in AML.

3.5.5 Summary of reimbursement documents

To date, only HAS, CVZ and SMC have issued a recommendation on Ceplene; HAS a positive one, CVZ and SMC a negative (Table 3.5-1).

HAS recommends HDC in spite of shortcomings of pivotal trial

The HAS report from 1 December 2010 briefly mentioned the methodological shortcomings of pivotal trial, but also recognised the absence of alternative maintenance treatments for AML patients and therefore gave a positive advice for the use of HDC in AML patients under 60 years in first remission that are ineligible for an allograft.

CVZ released the most extensive evaluation of HDC on 26 September 2011, about three years after the marketing authorisation. In the evaluation a lot of attention was given to the methodological shortcomings of study MP-MA-0201 and consequentially they concluded that the positive effects of HDC (five-month gain in leukaemia free survival, no significant difference in overall survival) were insufficiently supported. An important shortcoming was the absence of information on induction therapies and the great heterogeneity that could be expected in these induction therapies. Additionally the difference in effect on LFS between different countries, showed that the standard of care in a specific country was of influence on the LFS. Together with the fact that the study was performed between 1998 and 2002, this meant that there is great uncertainty if the chemotherapy received by patients in the study, corresponded with current practice.

CVZ does not recommend HDC for the treatment of AML

The SMC advice from 17 December 2010 is less extensive. Their main issues in the assessment of effectiveness were the lack of data on prior induction and consolidation regimens and on subsequent treatments following relapse, making the interpretation of the OS data problematic. Additionally, clinical experts indicated that the standard of care in AML had improved since the pivotal study was performed, hence HDC's potential place in therapy was unclear. The SMC also evaluated a cost-utility analysis submitted by the manufacturer and judged it to be insufficiently robust.

SMC does not recommend HDC for AML

Table 3.5-1: Main remarks on different aspects from the reimbursement evaluations of histamine dihydrochloride

	CVZ	HAS	SMC
Date	26.09.2011	01.12.2010	17.12.2010
Effectiveness	insufficient evidence	methodological weaknesses	considerable uncertainty
Safety	no fatal AEs	thrombocytopenia most serious AE	no fatal AEs
Cost-effectiveness	–	–	considerable uncertainty
Budget impact	–	–	up to £ 1,2m per year
Severity of disease	–	serious, life-threatening	–
Ease of use	self-administrable	–	–
Recommended	no	yes	no

Abbreviations: CVZ – College voor Zorgverzekeringen, HAS – Haute Autorité de Santé, SMC – Scottish Medicines Consortium, AE – adverse event

4 Discussion

This report aims to provide insight into the authorisation under exceptional circumstances of oncology drugs. Since the founding of the EMA in 1995, eleven oncologic drugs have been authorised under exceptional circumstances, seven of which received a regular marketing authorisation later on. The four drugs that are still licenced under exceptional circumstances were included in this report.

4.1 EMA's considerations and additional requirements

Two of the main questions we wanted to answer were; what were the main considerations of the CHMP to licence the included drugs under exceptional circumstances and what were the additional requirements for the marketing authorisation holder?

nelarabine and clofarabine have a very small target population

Two of the drugs, nelarabine and clofarabine, received a marketing authorisation under exceptional circumstances, clearly because of the very small size of the population. ALL and LBL are diseases which have gained better and better outcomes in the past decades and fortunately there are not that much patients in second relapse. Secondly, even in the absence of adequately controlled trials, nelarabine and clofarabine treatment achieved meaningful response rates and duration of response in a significant proportion of patients, said the CHMP. The really short life-expectancy in patients in second relapse and the possibility to reach long-term survival with both nelarabine and clofarabine followed by HSCT shows the actual benefit to patients. Of course there are many uncertainties regarding the safety profiles, but those should be tackled by the specific obligations required by the CHMP.

uncertainties regarding safety are addressed in specific obligations

For clofarabine the initial requests by the CHMP concerned only the user's information package and a voluntary adverse event reporting system. During the 3rd annually reassessment, additional obligations were added concerning population pharmacokinetics and dose adjustments in patients with moderate renal impairments. In the monitoring of adverse effects, extra attention was to be given to the monitoring of veno-occlusive disease after HSCT. For nelarabine the CHMP required data from an on-going phase III Children's Oncology Group study and a post-marketing surveillance study, to better define the safety profile. For both drugs there were no requirements concerning additional efficacy data, which reflects the opinion of the CHMP that they achieved meaningful responses.

publications on single-agent treatment are scarce

A review of the literature revealed barely any new information on single-agent treatment for the licenced indications, but fortunately clofarabine and nelarabine are currently tested in multiple multi-agent regimens in several clinical trials.

justification for authorisation under exceptional circumstances is unclear

Histamine dihydrochloride was authorised only after a re-examination and by majority decision, not by consensus. It was the only drug with a randomised phase III trial, owing to the much larger target population; patients with AML in remission. Rarity of the disease is therefore not clearly stated

as the ground for exceptional circumstances. In fact, the grounds for exceptional circumstances are not clear at all. Statistically significant results were only demonstrated for the surrogate endpoint leukaemia-free-survival, but not for overall survival.

For histamine dihydrochloride two additional studies were requested. A clinical study to evaluate the biomarkers and pharmacologic endpoints of histamine dihydrochloride plus low dose interleukin-2 in approximately 100 adults, to be completed in the second quarter of 2013 and a clinical study to evaluate minimal residual disease for the assessment of the anti-leukaemic activity of histamine dihydrochloride plus low dose interleukin-2 in approximately 150 adult patients, to be completed in the second quarter of 2013. This is in line with the uncertainties and disagreement regarding the efficacy. In favour of histamine dihydrochloride are the relatively mild side-effects. Information from clinicaltrials.gov and the EMA website is unfortunately suggesting that the progress in the compliance to the CHMP requirements is rather slow.

no additional publications at all

Specific obligations regarding two additional clinical trials

Trabectedin, like clofarabine and nelarabine, received its marketing authorisation under exceptional circumstances due to the rarity of the disease. The literature search however, implies that soft tissue sarcoma is not nearly as rare as ALL or LBL in second relapse. Subtypes of STS are indeed rare, and are considered too rare for adequately powered randomised controlled trials by the CHMP. What is contradictory to this statement is that trabectedin is licenced for all types of STS, although it was mainly tested in leiomyo- and liposarcoma. It is also not clear why it was not possible to perform a comparison to best supportive care. With respect to the safety of trabectedin, much more information was already available, since a lot of patients had been treated in compassionate use programs.

STS is less rare, but subtypes are

lack of comparison to best supportive care is not explained

For trabectedin the CHMP required the MAH to elucidate whether predictors of response to trabectedin in patients with soft tissue sarcoma could be identified. The final study report was to be submitted by 30 June 2012, but is still awaited by the EMA. Outside of the trials of the manufacturer, trabectedin has been tested in numerous clinical trials in the past few years and even extended its licence to a second indication. It is likely that more information will become available on the efficacy in different subtypes of STS.

specific obligations regarding predictors of response

Table 4.1-1: Compliance to additional requirements requested by the CHMP

	Clofarabine	Nelarabine	Trabectedin	Histamine dihydrochloride
Year of authorisation	2006	2007	2007	2008
Requirements for additional data	Safety and pharmacokinetic data	Safety data	Predictors of response	Biomarkers, pharmacologic endpoints and minimal residual disease
Delivered	Yes	Partly	No	No

4.2 Reimbursement evaluations

NICE and CVZ produce extensive evaluations, RIZIV and HAS are very brief

SMC is very concerned with cost-effectiveness

When analysing the reimbursement decisions, it becomes clear that CVZ and NICE put a lot more effort into their assessments than RIZIV, HAS and SMC. In the assessments of RIZIV, when it comes to effectiveness and safety, no opinion is given on the quality of the evidence at all; they consist merely of a short summary of outcomes and adverse effects. The assessments of HAS are a little more extensive, but not very critical either. Both agencies have not rejected any of the assessed drugs.

SMC does not perform really extensive evaluations, but is more critical of the submitted evidence on effectiveness, safety and cost-effectiveness. As they apply a strict cost-effectiveness threshold, not all the drugs were recommended. Clofarabine and nelarabine were recommended for restricted use, but histamine dihydrochloride and trabectedin were both not recommended.

The single technology evaluations of NICE are an extensive, but also time consuming process. The evaluation of trabectedin is very thorough and therefore provides an opportunity for trabectedin to be widely implemented into practice in England. The other three drugs have not been evaluated, but the publication by O'Connor et al, 2011 [44] shows that clofarabine is being used in England.

CVZ has evaluated three of the four drugs and recommended two of them. Their assessments are thorough and critical and separate the therapeutic and economic aspect. Drugs are not always recommended. As coverage with evidence development is always a condition for orphan or really expensive inpatient drugs, all drugs will be re-evaluated after about four years.

Table 4.2-1: Reimbursement decisions per agency

Reimbursement	Clofarabine	Nelarabine	Trabectedin	Histamine dihydrochloride
SMS	Restricted	Restricted	No	No
HAS	Yes	Yes	Yes	Yes
CVZ	Yes	NA	Yes	No
RIZIV	Restricted	Yes	Yes	NA
NICE	NA	NA	Yes, with PAS	NA

Abbreviations: CVZ – College voor Zorgverzekeringen, HAS – Haute Autorité de Santé, NICE – National Institute for Health and Clinical Excellence, RIZIV – Rijks Instituut voor Ziekte – en Invaliditeits Verzekering, SMC – Scottish Medicines Consortium, NA – Not applicable, PAS – Patient access scheme

4.3 Patient access and patient access schemes

There was only one patient access scheme identified. NICE recommended trabectedin after the manufacturer proposed a patient access scheme in which it is agreed that the acquisition costs of trabectedin for treatment needed after the fifth cycle are met by the manufacturer.

Coverage with evidence development is always required in the Netherlands for inpatient pharmaceuticals applying for additional financing. Usually this is paid for by the manufacturer, but in the case of trabectedin, the research is financed by The Netherlands Organisation for Health Research and Development. Since the request for additional financing of these drugs is done by the clinicians or hospital organisations and not by the manufacturer, it is not necessarily a patient access scheme.

In the end the most important question is if patients actually gained access to drugs through the market authorisation under exceptional circumstances. This can unfortunately not completely be extracted from just the reimbursement decisions. For the Netherlands and England a negative opinion does not strictly mean that a drug is not accessible, because hospitals can decide to pay for it. It is however unlikely. In the case that a drug is not assessed, access to it is rather unpredictable. In France, Belgium and Scotland however, a drug certainly needs a positive recommendation to be accessible.

In France all four drugs received a positive recommendation and nelarabine, clofarabine and trabectedin are on the T2A list for additional funding. This makes it very probable that French patients have access to all four drugs.

In Belgium the three drugs that were assessed, nelarabine, clofarabine and trabectedin, received a positive recommendation and are reimbursed. They are likely to be accessible for all patients. Histamine hydrochloride was not evaluated and is therefore not reimbursed. Although it is not as expensive as the other three drugs, it is unlikely that it's affordable to many of the patients.

NICE recommended trabectedin, which makes it mandatory to be available. Since England works with a negative list, the other three drugs are in theory reimbursable. Clofarabine has been used in practice, but it is not clear to which extent.

For Scotland it is more clear which drugs are available. Only nelarabine and clofarabine got a positive recommendation under specific conditions. Trabectedin and histamine dihydrochloride are very likely not accessible. Within the NHS system however, Scottish patients can travel to England to receive treatment. With the very strict cost-effectiveness criteria applied by the SMC, a lot of new medicines will likely not or with a delay be available in Scotland.

In the Netherlands a positive recommendation is not a necessity for treatment in the hospitals. Histamine dihydrochloride is an outpatient pharmaceutical and with the negative recommendation therefore not reimbursed. The conditional funding for trabectedin and clofarabine made the drugs accessible in certain academic hospitals. With the Netherlands being so small, they should be accessible to all patients. Nelarabine was not evaluated because it wouldn't reach the cost threshold for additional funding. Hospitals have the option to pay it from their budget.

one patient access scheme identified for trabectedin

coverage with evidence development is very common in the Netherlands

patient access cannot completely be extracted from reimbursement decisions

HAS recommended all four drugs

RIZIV recommended the three drugs it assessed

NICE evaluated one drug and recommended it

SMC recommended just two drugs with restrictions

CVZ recommended two of the three drugs it evaluated

4.4 Conclusions and recommendations

clofarabine and nelarabine are currently tested in multiple clinical trials and where always recommended when evaluated

With the authorisation of oncology drugs under exceptional circumstances the EMA has partially succeeded in providing safe and effective drugs to patients with very rare cancers. For nelarabine and clofarabine the additional clinical data up to now were limited, but several clinical trials are planned and the benefit to patients has been shown. When evaluated by reimbursement agencies, these two drugs always received a positive recommendation, which makes them accessible to patients.

for trabectedin a lot of new information has become available

For trabectedin a lot of new information has become available and the indication was even extended. The reason for the SMC to not recommend it, was the cost-effectiveness. For trabectedin it can be argued that the authorisation under exceptional circumstances wasn't completely justified, since STS is not as rare. The STS subtypes however, are.

HDC was only recommended in France and there are no additional publications

In the case of HDC the story is not that successful. The methodological weaknesses in the pivotal trial made CVZ and SMC issue a negative recommendation and the by the CHMP requested trials have still not been performed. Time will tell if histamine dihydrochloride can become a successful treatment.

the CHMP should be more clear about the justification for authorisation under exceptional circumstances

The criteria for authorisation under exceptional circumstances are not strictly defined, which gives the CHMP more freedom to apply this policy when they think it will be of benefit to the patient. This is acceptable, but a clearer statement of the justification is welcome. Additional requirements by the CHMP are often not met within the set time-frame.

It is clear that EMA and reimbursement agencies have a different perspective when they evaluate a drug. As innovative orphan drugs are introduced on the market, it cannot always be expected that they immediately prove their cost-effectiveness, they might be of great benefit to the patients however.

more collaboration between the industry, EMA and reimbursement agencies is needed in the development of drugs for very rare diseases

To retain the development of medicines for very rare diseases, it is important that industry, EMA and reimbursement agencies consult with each other. Scientific advice to the industry by EMA is highly recommended. Additionally the industry should pay more attention to the requirements of the 'fourth hurdle'; for example include the collection of utility data in the trial design, which is necessary for cost-effectiveness assessments. In return a new anti-cancer drug could be given some time to prove itself in clinical practice. Conditional coverage with evidence development, as performed in the Netherlands, seems a good option. The involvement of the clinicians is an advantage, since small pharmaceutical companies may not always have the expertise and financial means to perform this evidence development by themselves in a reasonable time-frame. It is then in the interest of the patient that the additional funding for this research is available. Since the patient populations in these cases are small, international collaborations are highly recommended. EU funding would then be a possibility.

conditional coverage with evidence development is a good option

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