Programme Européen de Formulations Orales Pédiatriques

European Program on Paediatric oral formulation

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O^3K project
Off-patent Oral Oncology drugs for Kids

Développement d'une formulation adaptée de Temozolomide
Développement d'une formulation adaptée de Cyclophosphamide

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O³K project Goals

- To develop **child-appropriate liquid formulations** of Cyclophosphamide and Temozolomide

- using NODS®, a new patent technology, as an **innovative oral drug delivery system for drinkable products** for children

- Providing Pk data for children of all ages

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Context

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The EU Pediatric Medicines Regulation *(EC1901/2006 Janv 2007)*

- **Requirement at the time of applications for new medicines for:**
  - **Data in children (as agreed by pediatric committee)**
- **Pediatric Investigation Plan (PIP)**
- **Reward:**
  - **6 months extension of supplementary protection certificate**
  - **2 years additional marker exclusivity (10+2) for orphan medicines**

For off-patent medicines specifically developed for children:

- **Specific Pediatric Use Marketing Autorisation (PUMA)**
  - **Enabling 10-years data protection**
  - **To stimulate research and development of off-patent products**

Contexte 2

EMEA Pediatric Expert Group (PEG)

- **List of paediatric needs of additional information for the use of off-patent medicines in children** *(EMEA/496777/2006 Rev.June 2007 EMEA/197792/2007)* **:**
  - **27 off-patent oncology products**
  - **9 of them are oral drugs that need age-appropriate formulation**

European Networks

ITCC: to conduct a comprehensive preclinical and clinical new drug development program

TEDDY Network: Task-force in Europe for the Drug Development for the young

CCLG Childhood Cancer and Leukemia Group (UK)

SIOP-EN: International Society of Pediatric Oncology

Contexte 3

7éme PCRD (Programme Cadre Recherche et Développement) ou FP7

FP7 call HEALTH-2007-4.2-1 : « adapting off-patent medicines to the specific needs of paediatric populations »

- Collaborative Projects
  ⇒ Multi-partner, multi-national research projects
- Annual average budget €7.22 billion, €54 million for Pedia-Onco

http://cordis.europa.eu/fp7/

HEALTH 2007 A 1.2.0.0 1: Adapting off patent medicines to the specific needs of paediatric populations. Support will be given to clinical studies dedicated to provide evidence for specific paediatric use of off patent medicinal products currently used off label . Studies include the assessment of pharmacokinetics data, of efficacy and safety, and/or the development of appropriate formulations.**Funding scheme:**Collaborative Project with a maximum EC contribution of €3,000,000/project.

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Génèse

Génèse 1

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Médecin-Pédiatre Directeur Recherche Clinique & Translationnelle

- Expert pour le COMP ou PDCO EMEA
- Président de ITCC
- Membres de SIOP et Network européens d'Onco-pédiatrie

Liste des besoins en formes galéniques adaptées et en information Pk de l'EMEA

Annex 4: Pharmacokinetic (PK) data in paediatric age groups

Active substance (EMEA-PEG list)	PK	Age	Priority
Melphalan	Yes	0-18	0
Ciclophosphamide	Yes	2-18	1 (< 1 yrs)
Chlorambucil	No	-	0
Actinomycin D	Yes	< 21	1 (< 1 yrs)
Ifosfamide	Yes	1-18	0
Dacarbazine	No	-	1
Temozolomide	Yes	0-21	0
Carmustine	No	-	0
Lomustine	No	-	1
Cisplatin	Yes	0-18	0
Carboplatin	Yes	0-18	0
Oxaliplatin	No	-	2
Bleomycin	Yes	Children	0
Methotrexate	Yes	> 3 mos	0
Thiotepa	Yes (only in CSF)	Children	2
Fludarabine	Yes	Children	0
Mercaptopurine	Yes	Children	0
Thioguanine	Yes	Children	0
Cytarabine	Yes	Children	0
Liposomal cytarabine	Yes (only in CSF)	>3	0

Annex 2.4: Age formulation

Active substance	Age formulation	MS availability
Melphalan	X	
Cyclophosphamide	X	X
Chlorambucil	X	X
Temozolomide	X	
Carmustine	X	X
Lomustine	X	
Methotrexate	X	
Mercaptopurina	X	
Thioguanina	X	
Mitoxantrone	X	
Etoposide	X	
L-asparaginase/PEG-asparaginase		X

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Annex 2.1: Requested studies for extending the existing indication

Active substance	Requested studies for extending the existing indication	Expert opinion (0;1;2)	Comment and suggestions
Cyclophosphamide	PK/efficacy/safety < 1 yrs	1 (for PK only)	Largely, safely and efficaciously experienced in children of all ages except PK< 1 yrs
Dacarbazine	efficacy/safety in not-studies ages	0	Use limited to Hodgkin disease(HD), exceptional in younger children
Temozolomide	efficacy/safety < 3 yrs	2	It is great interest in refractory solid tumours, other brain tumours in all pediatric ages
Lomustine	efficacy/safety in not-studies ages	0	Use limited to medulloblastoma > 3 y of age. No use expected for children < 3y of age so far
Bleomycin	efficacy/safety in not-studies ages	0	Use limited to HD, germinal and non germinal tumours of 0-18 yrs
Methotrexate	efficacy/safety in infants < 6 months	0	Largely, safely and efficaciously experienced in children of all ages with different tumors types
Mercaptopurine	Pharmacogenetic (TPMT genotype value)	0	Genetic variation in response (polymorphisms) is already consistently evaluated
Thioguanine	Pharmacogenetic (TPMT genotype value)	0	Genetic variation in response (polymorphisms) is already consistently evaluated
Cytarabine	efficacy/safety < 3 yrs	0	Largely, safely and efficaciously experienced in children of all ages with ALL, AnLL, NHL
Liposomal cytarabine	PK/efficacy/safety < 18 yrs	2	Limited experienced of the drug in all pediatric ages, but of interest in neoplastic meningitis
Idarubicin	efficacy/safety in not-studies ages	1	Largely, safely and efficaciously experienced in children of all ages with ALL, AnLL
Mitoxantrone	efficacy/safety < 18 yrs	0	Already experienced in children with AnLL aged 0-18 yrs
Vincristine	efficacy/safety in not-studies ages	0	Largely, safely and efficaciously experienced in children of all ages with different tumors types
Vinblastine	efficacy/safety in not-studies ages	1	Largely experienced in HD. Additional indication in Langherans cells tumor and acute large cell lymphoma (ALCL) of 0-18 yrs of age
Vindesine	efficacy/safety in not-studies ages	1	Recent experience in NHD and ALL of 0-18 yrs of age
Procarbazine	efficacy/safety in not-studies ages	0	Use limited to HD in children of 0-18 yrs of age
Doxorubicin	efficacy/safety in not-studies ages (including newborns)	1	Safely and efficaciously experienced in children of all ages with different tumors types
Liposomal doxorubicin	efficacy/safety in not-studies ages (including newborns)	2	Little experienced in all paediatric ages, but of interest in many types of paediatric tumours
Daunorubicin	efficacy/safety in not-studies ages (including newborns)	1	Safely and efficaciously experienced in children of all ages with different tumors types
Melphalan	Update SPC with PK and other date in AL and neuroblastoma > 3 months	0	It is mainly used in the conditioning regimen for Haemopoietic Stem Cell (HSC) transplantation in children of all age groups. Meaningful likelihood of a transplant < 3 months of age due to time to transplant since onset of disease and time for unrelated donor search

« Artisanat Pharmacotechnique Hospitalier »

PH dans sa PUI

Problématique

1. Protocole associant le cyclophosphamide (CPM) à la dose de 25 mg/m² et la Navelbine (NVB) pour traiter les rhabdomyosarcomes de l'enfant.

2. Formes disponibles : CPM per os comprimés dosés à 50 mg
   CPM IV dosé à 500 mg ou à 1g

? Solutions apportées

1. Gélules à partir de la poudre pour perf IV -> quid enfant qui n'avale pas?
2. Reconditionnements à partir de la solution reconstituée pour perfusion IV >stabilité réduite et quid tolérance GI?.

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Structuration

9 partners from 3 European states (UK, Italy & France) including

- 5 institutions
  - Institut Gustave Roussy (IGR), France (Coordinator)
  - Northern Institute for Cancer Research (NICR), Univ. of Newcastle, UK
  - Institute of Cancer Research (ICR) / Royal Marsden, UK
  - Università Cattolica-Policlinico Gemelli (UCSC) / Roma, Italy
  - University Hospitals of Leicester NHS Trust (ULEIC), UK

- 3 SMEs (Small-Medium Enterprise)
  - Oralance, France (Technology)
  - Keocyt, France
  - Negositek, France

- 1 Parents Organisation
  - UNAPECLE (Ethics)

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WorkPackages

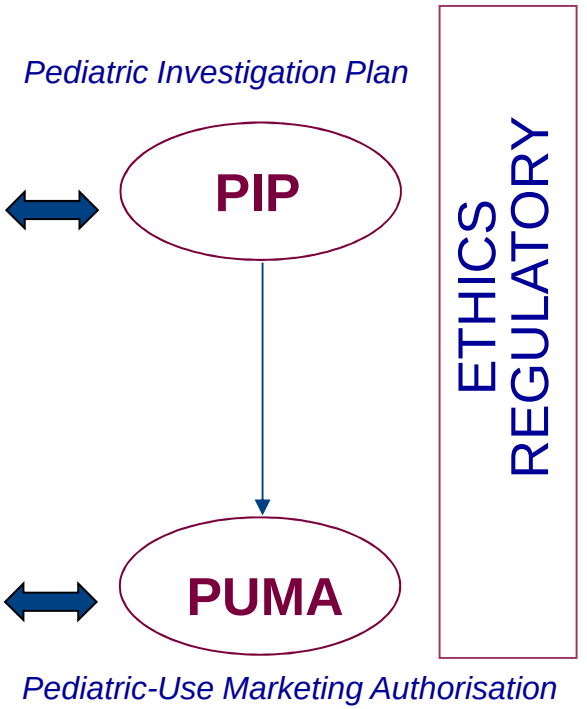
WP 1: Consortium Management

WP 2: Preclinical and Pharmaceutical Development

WP 3: Formulation, Supply & Regulatory

WP 4: Clinical Studies

WP 5: Pharmacokinetic Evaluation



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Techno

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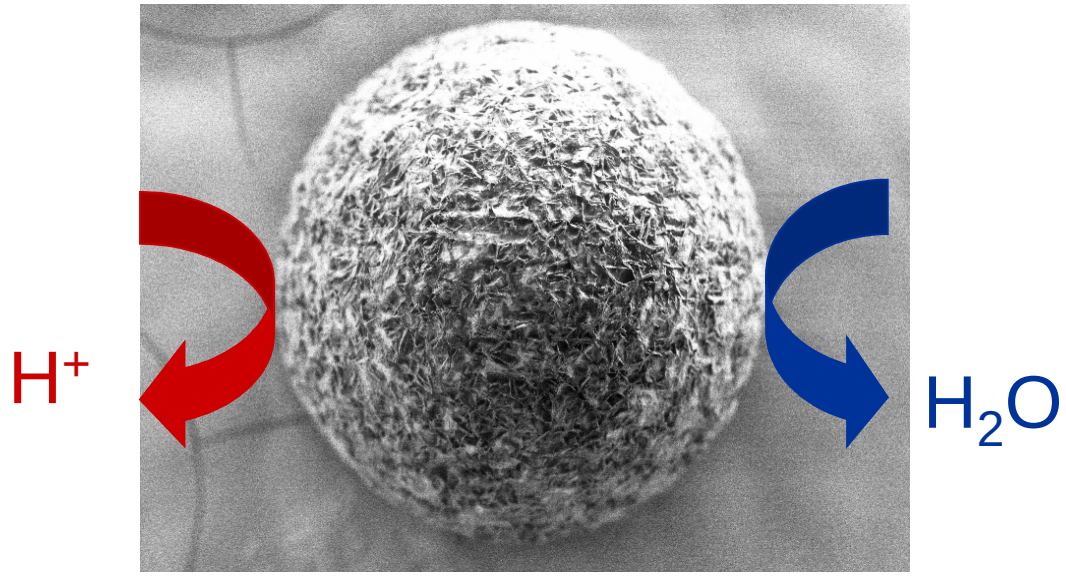
Drug entrapment in NODS® particle (Oralance)

- ✓ Particles stable in aqueous and gastric conditions
- ✓ Compatibility with insoluble compounds
- ✓ Only pharmaceutical agreed excipients (GRAS/FDA)



NODS®

New Oral Delivery System

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NODS® Simultaneous properties

- ✓ Lipophilic drug solubilization
- ✓ Gastroprotection
- ✓ Stabilization
- ✓ Chemical protection of labile drugs
- ✓ Taste making

→ **Suprabioavailability**

Taste masking

SAFE, TASTE MASKED AND BIOAVAILABLE
LIQUID OR DRY FORM

Safe technology - Safe product

All compounds are regulatory approved : PE – USP

All compounds are safe : GRAS/FDA List

Solvent free process

Surfactant free products

Suitable for any final product

Syrups, Suspensions,

Oral powder

Dry syrups

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⇢ Development of NODS®Cyclophosphamide

CYCLOPHOSPHAMIDE (Date of the MA granting : 19/06/1970)

As provided by Endoxan® french SPC:

- *Cyclophosphamide is used in leukaemias, lymphomas, soft tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular, breast and lung carcinomas for its immunosuppressive properties in non malignant diseases, especially autoimmune and inflammatory diseases, such as lupus, polymyositis, rheumatoid arthritis, dermatopolymyositis.*

- *IV administration:*
  - adults : 500 and 4000 mg/m² every 3 weeks
  - children : 150 and 1200 mg/m² every 3 weeks

- *Oral administration:*
  - adults and children 100 to 200 mg/m², 2 weeks out of 4
  - adults and children 40 to 100 mg/m² continuously

Oral CYCLOPHOSPHAMIDE in paediatric daily practice

- **Replacement of IV formulation** in some combination regimens (e.g. CADO in Neuroblastoma)
- In **palliative setting** to control symptoms
- **Protracted low dose 25 mg/m² daily** in combination with Vinorelbine in relapsed pediatric sarcoma (Casanova et al. 2004; ongoing confirmatory phase II trial in France)
- ongoing European randomized phase III trial in high-risk rhabdomyosarcoma in children evaluates the use of a maintenance therapy, composed of vinorelbine (iv weekly 25 mg/m²) and cyclophosphamide (oral daily 25 mg/m²) for 6 months, versus no further treatment in children in complete remission after chemotherapy and surgery.
- in several so-called “metronomic” therapies in paediatric malignancies (Stempak; 2006), as well as in adult cancers (Kesari, 2007; Orlando, 2006).

Oral CYCLOPHOSPHAMIDE on a daily practice

- Commercially available 50mg tablets are not suitable for children who cannot swallow, especially children below the age of 6.

- The daily dose of 50 mg/m² cannot be delivered to each child depending on patient age and body weight

- "Artisanat Pharmaceutique" *J. Pharm. Biomed. Analysis 38 (2005) 180-185*:
  - IV powder for capsule preparation at 10 and 25 mg
  - Analytical control by HPTLC
  - Stability study in capsule over 60 days
  - Drawbacks: need to open the capsules for children who cannot swallow!

- "Artisanat Pharmaceutique" :
  - IV solution given orally at 20 mg/mL in glass vials
  - Adequate volume according to prescription
  - According to literature, stable for 14 days at 4° C
  - Drawbacks: Handling at home? Into the fridge with food? Bioavailability? GI tolerance?

NODS® CPM in O3K project

- **Goal**: To provide an oral formulation for protracted daily administration of cyclophosphamide in children, whatever their age is
  - Liquid form
  - Prolonged stability
  - Good (improved?) Bioavailability
  - No taste
  - Safe for the environment (family and nurses)

- **Intended indications** :
  The current indications of IV/oral cyclophosphamide in children i.e. leukaemia, lymphoma, soft tissue and osteogenic sarcomas, paediatric malignancies, along with non malignant diseases
  Children from 6 months of age.

- **NODS®CPM product** :
  dry powder in glass vials to be reconstituted in water.
  Final suspension of cyclophosphamide at 10mg/mL

NODS®CPM Development plan (Paediatric Investigation Plan)

Pharmaceutical part :

1. **Description of the final product**
   Dry powder of NODS® microparticles containing cyclophosphamide (NODS®CPM) packaged in amber glass
2. **Composition of the final product**
   Cyclophosphamide and semi-synthetic glycerides (FDA/GRAS)
3. **Manufacturing process**
   Cyclophosphamide incorporation in NODS®
4. **Controls**
   Cyclophosphamide and excipients
5. **Stability**
   Cyclophosphamide in NODS® and reconstituted suspension for regulatory authorities
6. **Bioavailabilty**
   In vitro comparative bioavailability study comparing cyclophosphamide in NODS®CPM to the available oral form

NODS®CPM development plan (Paediatric Investigation Plan)

Clinical part :

- A ***Pk and safety*** trial comparing the developed liquid form to the currently available IV form in paediatric patients with recurrent or refractory malignant solid tumours.
- Patients to receive 1 cycle of 50 mg/m² daily
- Assay of cyclophosphamide and metabolites by LC/MS (WP 5)
- Absolute (cohorte 1) and relative (cohorte 2) bioavailability

Children between 6 months to 6 yrs	Group 1	Group 2
n	12	12
Day 1 (PK sampling)	IV CPM 50mg/m² over 1h	NODS®CPM 50mg/m²
Day 2 (PK sampling)	NODS®CPM 50mg/m²	IV CPM 50mg/m² over 1h
Day 3-21	NODS®CPM 50mg/m²/d	NODS®CPM 50mg/m²/d

randomization

Children over the age of 6	Group 1	Group 2
n	15	15
Day 1 (PK sampling)	Tablets Endoxan® 50mg/m² over 1h	NODS®CPM 50mg/m²
Day 2 (PK sampling)	NODS®CPM 50mg/m²	Tablets Endoxan® 50mg/m² over 1h
Day 3-21	Tablets Endoxan® 50mg/m²/d	NODS®CPM 50mg/m²/d

⇢ Status

- Started in sept 2008
- 9 months delayed for formulation difficulties

⇢ Rendez-vous

- January 2011 for CPM clinical studies
- June 2012 (hopefully)
  - PUMA
  - Child-appropriate formulation for child

Many thanks for your attention