Smart Pharma
CONSULTING

Rare Diseases on the French Market

Market Insights

Case study: Narcolepsy

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Smart Pharma Consulting proposes a review of rare diseases management on the French Market with the implications for pharma companies and the specific study of the narcolepsy

Introduction

Context

- With 3 million people affected in France (i.e., 4.4% of the population), rare diseases are a major public health issue
- 50% of people concerned benefit from a proper diagnosis
- 25% of them must wait, on average, 4 years before getting a reliable diagnosis
- For 95% of the ~7,000 rare diseases identified, there is no curative treatments

Objectives

- The objectives of this study are to:
  - Review the conditions of rare diseases management…
  - … and of market access for orphan drugs in France
  - Analyze the organization of the different stakeholders
  - Illustrate the current situation through the study of one rare disease: the narcolepsy

Methodology

- Overview of the rare disease market in France:
  - Rare diseases prevalence
  - Rare disease management and healthcare organization
  - Market access conditions of orphan drugs
  - Market challenges and KSFs for pharma companies
- Case study: Narcolepsy :
  - Disease definition
  - Stakeholders: mapping and analysis
  - Market size, structure and dynamics (2019 – 2023)
  - Market drivers and limiters

Sources: Agence Nationale de la Recherche (website 2024) – Smart Pharma Consulting analyses

Rare diseases prevalence is defined as < 1/2,000 affected individuals, corresponding to ~3,000 patients in France, for which pharma companies try to develop orphan drugs

Definitions

	European Union	France
Rare diseases	▪ Definition: population **< 1/2,000** ▪ Prevalence: ~ **36 million** patients	▪ Definition: population **< 1/2,000** ▪ Prevalence: ~ **3 million** patients
Orphan drugs	▪ Drugs for **prevention**, **diagnosis** or **treatment** of **rare diseases**, which respond to **public health need** ▪ **Low expected sales** may **prevent** pharma companies to **develop** orphan drugs under **normal market conditions** ▪ **European regulation**[1] promotes **research**, **development** and **marketing** of orphan drugs	
Orphan diseases	▪ Diseases **not adopted** by pharma companies as they provide **little financial incentive** for the private sector: – **Rare diseases** – **Common diseases** that have been **ignored** (e.g.; tuberculosis, cholera, typhoid, malaria) as they are more prevalent in developing countries than in the developed world	

Sources: Orphanet (March 2024) – French Ministry of Labor, Health and Solidarities (July 2023) – European Commission (March 2024) – Smart Pharma Consulting analyses

[1] *N° 141/2000 voted by the European Parliament in December 1999*

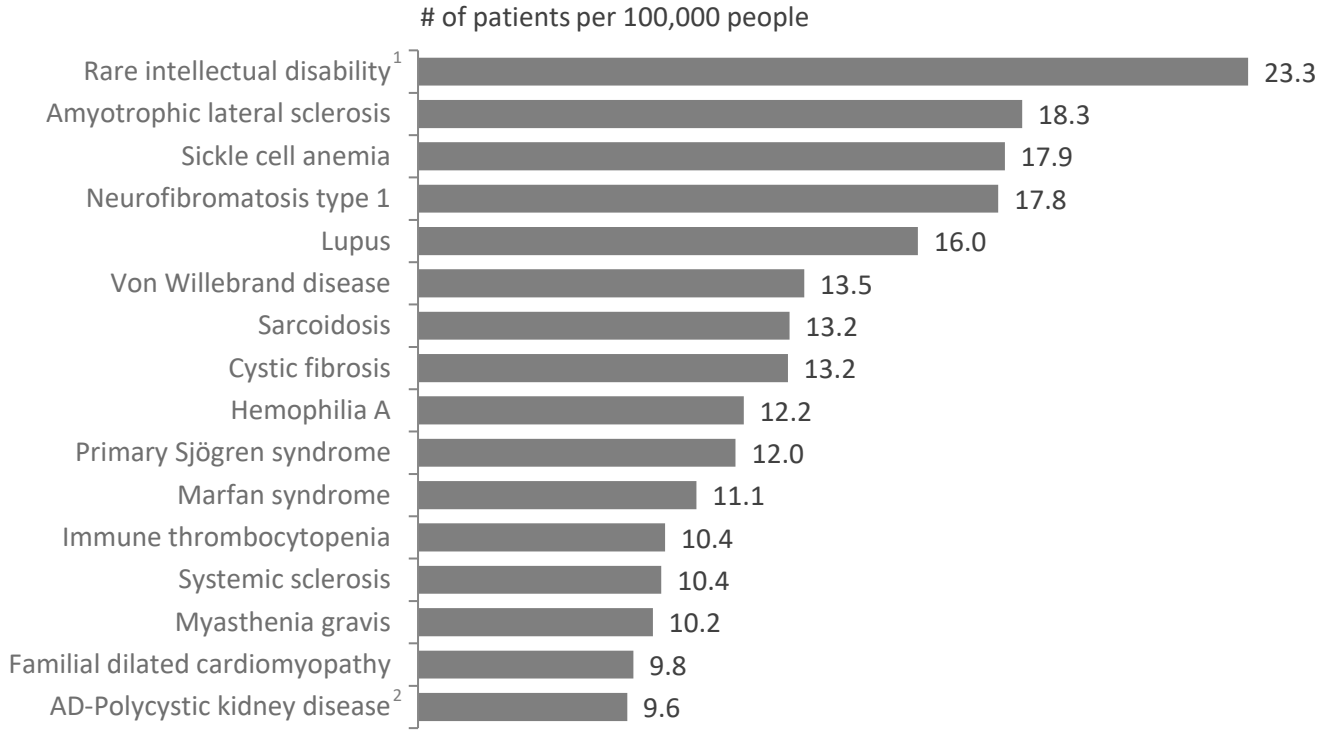
Prevalence rates per condition are low and may be underestimated due to difficult diagnosis, but their collective impact on population and healthcare systems is significant

Rare diseases overview

EU key figures (2023)

- **~36 million** patients
- **~7,000** existing rare diseases
- **~80%** of rare diseases are of **genetic** origin
- **~5%** of rare diseases treated with **~ 200 approved** drugs
- **~70%** of rare diseases starting in **childhood**
- **60%** of **approved orphan drugs** are for **pediatric** use

Most prevalent rare diseases in France (2023)



Note: ~400 million patients suffering of rare diseases in the world

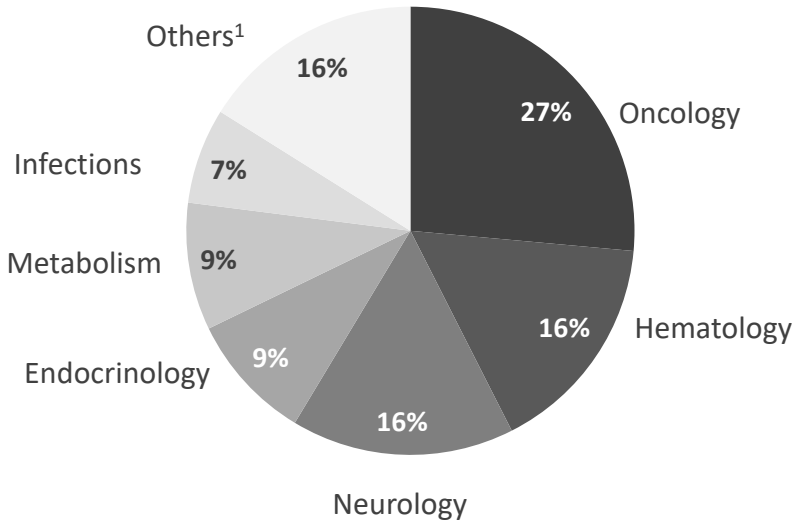
Sources: Banque Nationale de Données Maladies Rares (Nov. 2023) – European Commission (March 2024) – Global Genes (March 2024) – Smart Pharma Consulting analyses

[1] Non-syndromic – [2] Autosomal dominant polycystic kidney disease

Oncology, hematology and neurology are the three top therapeutic areas of rare diseases treated, accounting for ~59% of EMA orphan drugs approvals between 2019 and 2023

Main therapeutics areas covered by orphan drugs (2019-2023)

Distribution of 2019-2023 EMA orphan drugs approvals by therapeutic area



Rare diseases – by therapeutic areas – for which orphan drugs have been approved

- **Oncology:** most approvals concern drugs for blood cancers (e.g.; AML[2], CML[3], DLBCL[4], MCL[5]), gastrointestinal cancers, glioma or multiple myeloma
- **Hematology:** anemia, hemophilia, myelofibrosis or sickle cell disease
- **Neurology:** Duchenne muscular dystrophy, Friedreich's ataxia, Lennox-Gastaut syndrome, generalised myasthenia gravis or spinal muscular atrophy
- **Endocrinology:** acromegaly, acute hepatic porphyria, chronic hypoparathyroidism, Cushing's syndrome or growth hormone deficiency
- **Metabolism:** acid sphingomyelinase deficiency, Hutchinson-Gilford progeria syndrome, hyperargininemia or phenylketonuria
- **Infections:** chronic long-term hepatitis delta virus, cytomegalovirus, inhalational anthrax or invasive candidiasis

Sources: "Human medicines highlights", EMA (2019-2023) – Eurordis (March 2024) – Smart Pharma Consulting analyses

[1] Incl. allergology, dermatology, gastroenterology, hepatology, immunology, nephrology, ophthalmology, pneumology, rheumatology, transplantation and uro-nephrology – [2] Acute Myeloid Leukemia – [3] Chronic Myeloid Leukemia – [4] Diffuse large B-cell lymphoma – [5] Mantle cell lymphoma

Drugs should be granted the orphan designation by the COMP[1] (EMA[2]), then a centralized market authorization, before being approved by the ANSM[3] (which can also authorize an early access)

Market access – Marketing authorization

EMA

- On December 16, 1999, the European Parliament established the **COMP**, EMA's responsible **committee** for evaluating **applications** for **orphan designation**
- The COMP is committed to evaluate within 90 days whether the **orphan designation criteria** are met:
  - The drug must **treat**, **prevent** or **diagnose life-threatening** or **chronically debilitating** conditions
  - The **prevalence** of the disease must be ≤ **1 in 2,000** in the EU or it is **unlikely** that marketing the drug would generate sufficient **returns** to justify the required **investment**
  - The drug **must be of significant benefit** to the patients
- Drugs designated as **orphan[4] benefit from:**
  - **Protocol assistance**
  - **10-year** marketing **exclusivity[5]**
- Marketing application is then submitted to the EMA's CHMP (Committee for Medicinal Products for Human Use)

ANSM

- On March 31, 2004, the European Parliament determined that **all marketing authorizations** for **orphan medicines** in the EU had to follow the **centralized authorization**
- However, although the centralized procedure grants authorization in all European Union members, there is **no obligation** to market the drug in every Member State
- In France, the **ANSM** is responsible for issuing **marketing authorization**, based on a **benefit/risk** assessment
- Since July 2021, an **Early Access Authorization** (AAC[6]) can be granted to innovative drugs by the HAS[7], based on the ANSM's opinion on the presumptions of efficacy and security of the product
- Innovative **orphan** drugs are concerned by this AAC if there is **no other appropriate treatment available**, and if the **treatment cannot be delayed**

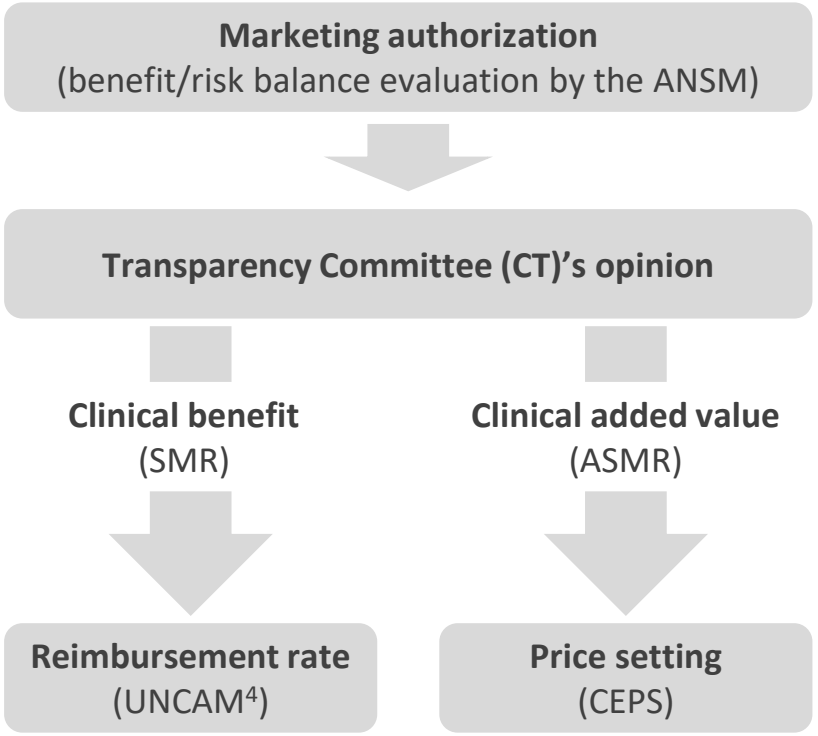
Sources: EMA website (March 2024) – Orphanet website (March 2024) – ANSM website (March 2024) – Smart Pharma Consulting analyses

[1] Committee of Orphan Medicinal Products – [2] European Medicines Agency – [3] Agence Nationale de Sécurité du Médicament – [4] Reassessment every 6 years – [5] In case of pediatric use, which corresponds to 60% of the orphan drugs, the marketing exclusivity is extended to 12 years – [6] Autorisation d'Accès Compassionnel – [7] Haute Autorité de Santé

After being granted their marketing authorization by the ANSM[1], orphan drugs should be evaluated by the Transparency Committee[2] before negotiating their price with the CEPS[3]

Market access – Pricing and reimbursement

Market access process in France



Transparency Committee (CT)

- In France, an orphan drug benefits from an **accelerated procedure**, reduced from **90** to **30 days** after dossier depot
- Orphan drugs **do not have** to present a **direct comparison** to another drug in their clinical trial to get the CT's opinion
- Regardless of the clinical added value (ASMR), orphan indications are covered by the **long-term illness provision** (ALD[5]) which grants full reimbursement of treatment

Economic Committee on Healthcare Products (CEPS)

- The **amendment** of the **framework agreement** signed in **April 2022** between the **CEPS** and the **LEEM**[6] streamlined pricing negotiations for **orphan drugs**:
  - **Relevant pricing comparators**[7] clarification
  - Possibility to set a **capped budget**[8]
  - **Price revision** if the number of patients evolves
  - **CEPS** authorization to be supported by **medical experts**

Sources: Transparency Committee website (March 2024) – CEPS website (March 2024) – National Health Insurance website (March 2024) — Smart Pharma Consulting analyses

[1] Agence Nationale de Sécurité du Médicament – [2] Commission de Transparence – [3] Comité Economique des Produits de Santé – [4] Union Nationale des Caisses d'Assurance Maladie – [5] Affections Longue Durée – [6] Les Entreprises du Médicament – [7] They must have the same indication as the orphan drug and be patent-protected – [8] To allow patient access to innovation while guaranteeing pharma companies list prices consistent with international prices

The rare diseases plans (PNMRs[1]) introduced by French health authorities for almost 2 decades aim to improve the diagnosis and the management of patients suffering from rare diseases

Rare diseases plans

2003
Law establishing PNMRs

PNMR1

- Identification of **expert centers** in rare diseases
- Establishment of **orpha.net**, portal dedicated to rare diseases

PNMR2

- Improvement of **patient journey**
- Establishment of **rare diseases healthcare networks** …
- … Through the labeling of 23 **FSMRs**[2]
- Setting up of **European networks**

PNMR3

- **Observatory** to fight against diagnostic wandering
- Creation of the national rare disease database (**BNDMR**[3]) to register patients
- Renewal of the labeling of **reference** and **competence centers**[4]

PNMR4*

- **Office-based HCPs' information** & **training**
- **Reduction** of **diagnostic wandering**
- Improved **life** and **care journey**
- **Access** to **treatments** and **innovations**
- **Database interoperability**

2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024

** PNMR4 launch expected in 2024*

Sources: French Ministry of Labor, Health and Solidarities (March 2024) – filieresmaladiesrares.fr (March 2024) – Smart Pharma Consulting analyses

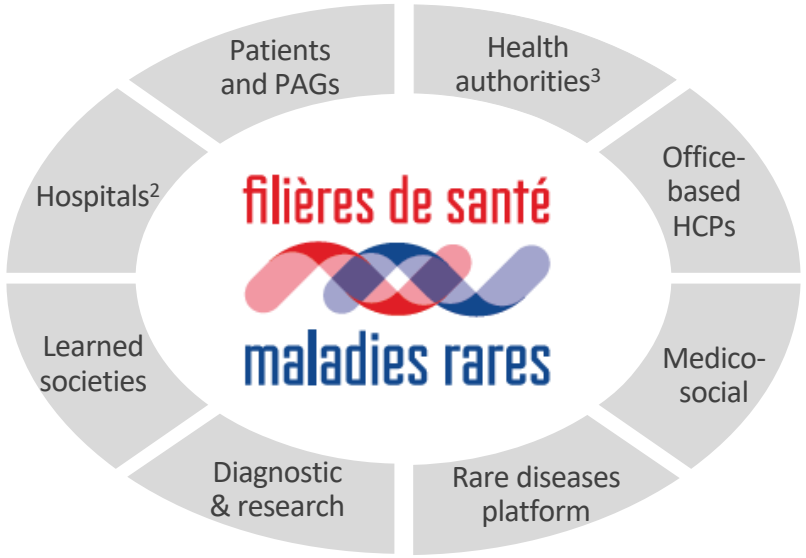
[1] Plan National des Maladies Rares – [2] Filières de Santé Maladies Rares – [3] Banque Nationale de Données Maladies Rares – [4] 2,311 centers as of March 2024 (in both mainland and overseas France)

Rare diseases healthcare networks (FSMRs[1]) ensure the coordination between each key stakeholder involved in the management of patients suffering from rare diseases

Rare diseases healthcare networks – Introduction

Description

- As part of the **PNMR2**, **23 FSMRs** are labelled in France
- Attached to **hospitals** and placed under the responsibility of **medical managers**, they **coordinate** a set of actors involved in the management of rare diseases patients:



Missions

#1
- **Improve patient management**
(e.g., development of epidemiological databases, initiatives to increase diseases awareness, medical practices harmonization, directories of experts)

#2
- **Coordinate and encourage research**
(e.g., fundamental, translational or clinical research)

#3
- **Inform and train**
(e.g. seminars or e-training to HCPs, communication to the general public, patients or their relatives)

#4
- **Participate in European healthcare networks**
(e.g. collaboration with rare diseases healthcare networks of other European countries)

Sources: filieresmaladiesrares.fr (March 2024) – Smart Pharma Consulting analyses

[1] Filières de Santé Maladies Rares – [2] Incl. reference and competence centers – [3] Incl. French Ministry of Labor, Health and Solidarities or regional health agencies

Each of the 23 rare diseases healthcare networks (FSMRs[1]) labeled in France has been built around a set of rare diseases with common aspects

Rare diseases healthcare networks – Mapping

filières de santé maladies rares

1 AnDDI-Rares — Development anomalies & intellectual disabilities

2 BRAIN-TEAM Filière Nationale de Santé Maladies rares du système nerveux central — Rare diseases of the central nervous system

3 cardiogen filière nationale de santé maladies cardiaques héréditaires ou rares — Hereditary or rare heart diseases

4 DéfiScience Maladies Rares du Neurodéveloppement FILIÈRE NATIONALE DE SANTÉ — Brain development & intellectual disabilities

5 Fai2r — Autoinflammatory & autoimmune diseases

6 FAVA-MULTI — Vascular diseases with multisystem involvement

7 FILFOIE FILIÈRE DE SANTÉ MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT — Rare liver diseases in children and adults

8 Filnemus Filière Neuromusculaire — Neuromuscular diseases

9 FILSLAN — Amyotrophic lateral sclerosis

10 fimarad — Rare dermatological diseases

11 FIMATHO Filière Santé Maladies Rares — Abdomino-thoracic malformations

12 FIRENDO — Rare endocrine diseases

13 G2M — Hereditary metabolic diseases

14 MaRIH — Rare immuno-hematological diseases

15 MCGRE — Red blood cells & erythropoiesis diseases

16 MHEMO La Filière des maladies hémorragiques constitutionnelles — Constitutional Hemorrhagic diseases

17 Filière MUCO CFTR — Cystic fibrosis & CFTR[2] abnormality

18 NeuroSphinx FILIÈRE SANTÉ MALADIES RARES — Rare pelvic & spinal cord malformations

19 ORKiD — Rare kidney diseases

20 OSCAR — Rare diseases of bone, calcium & cartilage

21 RespiFIL Filière Maladies Respiratoires Rares — Rare respiratory diseases

22 SENSGENE Maladies Rares Sensorielles — Rare sensory diseases

23 FILIÈRE SANTÉ MALADIES RARES TeteCou MALFORMATIONS RARES TÊTE COU DENTS — Rare diseases of the head, neck & teeth

Sources: filieresmaladiesrares.fr (March 2024) – Smart Pharma Consulting analyses

[1] Filières de Santé Maladies Rares – [2] Cystic Fibrosis Transmembrane conductance Regulator

Founded in 2001 and financially supported by the AFM-Téléthon and French public funds, the rare diseases platform promotes synergies to advance the fight against rare diseases

Rare diseases platform

Description

- Platform **created in 2001** and **financially supported** by:
  - The **AFM-Téléthon**
  - The **French Ministry of Labor, Health and Solidarities**
- It **brings together** at the **Hospital Broussais** in **Paris**:
  - **Health** and **research professionals**[1]
  - Representatives of **PAGs**
  - Over a hundred of **employees** and many **volunteers**[2]
- Its **objectives** are to:
  - Have rare diseases recognized as a **public priority**
  - Support the creation and activity of rare diseases **PAGs** (e.g., training, information sharing and mutual support)
  - Develop **knowledge** and **information** for all audiences
  - Support and strengthen **research** on rare diseases
  - Offer **meeting-** and **work-spaces** for all stakeholders involved in the fight against rare diseases (e.g., ~450 meetings held in 2022 with ~6,000 participants)

Members

- **Six autonomous entities** form the platform:

AFMTÉLÉTHON – INNOVER POUR GUERIR *Founder of the platform and main funding entity*	Alliance maladies rares – UNIS POUR VAINCRE *French collective of 240 PAGs*
EURORDIS – RARE DISEASES EUROPE *European federation of over 1,000 PAGs from 74 countries*	FONDATION maladies rares *Foundation bringing together researchers & HCPs*
MALADIES RARES INFO SERVICES *French service providing support & information on rare diseases*	orphanet – Inserm *Reference portal for rare diseases and orphan drugs*

Sources: Rare disease platform website (March 2024) – Alliance Maladies Rares website (March 2024) – Eurordis website (March 2024) Smart Pharma Consulting analyses

[1] E.g., physicians, geneticists, epidemiologists – [2] Specializing in the support for patients and families, information, IT, communication, support for associations, etc.

Narcolepsy which is characterized by excessive daytime sleepiness, with or without cataplexy, if properly diagnosed, can be treated by more or less specific drugs

Narcolepsy: Definition & Guidelines

CASE STUDY

Definition & Diagnosis

- **Chronic** disease, often starting during **childhood**
- Caused by **the loss of hypocretin neurons** and **low orexin A levels** in the cerebrospinal fluid
- Several **symptoms** can lead to suspicion of narcolepsy[1]:
  - Consistent ones: excessive daytime sleepiness
  - Inconsistent ones: hallucinations, sleep paralysis
- Narcolepsy are of two types:
  - **Type 1**: with cataplexy (loss of muscle tone)
    → Daily willingness to sleep during daytime for at least 3 months and tests
    → Cataplexy revealed by polysomnography or cerebrospinal fluid analyses
  - **Type 2**: without cataplexy
    → Diagnosis of exclusion based on at least a polysomnography and a Multiple Sleep Latency Test

Treatment

- Pharmacological solutions:
  - **Psychostimulants** and **antidepressants**[2] indirectly increase the levels of neurotransmitters (e.g., dopamine, noradrenaline)
    → Improve wakefulness & reduce sleepiness
  - **H3 histamine receptor antagonists** increase histamine concentration and activity in the brain
    → Improve wakefulness & reduce the frequency of cataplexy attacks
  - **CNS depressants** slow down brain activity by increasing the production of GABA neurotransmitter
    → Reduce the frequency of cataplexy attacks
- Non-pharmacological solutions: **lifestyle modifications**
- **Comorbidities** (metabolic, psychiatric, obstructive sleep apnea) are also to be treated

Sources: Plan National de Diagnostic et de Soins (Sept. 2021) – Smart Pharma Consulting analyses

[1] Diagnosis in children is based on the changes of habits of sleep and behavior (usually a hyperactivity disorder arises) – [2] Such as venlafaxine, fluoxetine and citalopram

Narcolepsy which affects ~20K-30K patients in France, is handled in specialized centers by neurologists and psychiatrists who have a limited number of drugs at their disposal

CASE STUDY

Narcolepsy: Stakeholders mapping

Market Access

- Marketing authorization:
  - Granted by the **EMA** (European Medicines Agency) for EU countries and then…
  - … transposed by the **ANSM**[1] for France
- Health technology assessment carried out by the **HAS**[2] based on the:
  - Clinical benefit (SMR)
  - Clinical added value (ASMR)
- Pricing decision by the **CEPS**[3]
- Reimbursement decision by the **UNCAM**[4]

Drugs prescribed

Mode of action	Type 1 narcolepsy	Type 2 narcolepsy	Hypersomnia & type 1 or 2 narcolepsy
Psycho-stimulant	▪ Methylphenidate[7] ▪ Amphetamines[7] ▪ Solriamfetol[8]		Modafinil
CNS depressant	Na oxybate		
Histamine receptor antagonist	Pitolisant		

Healthcare professionals (HCPs)

- 7 Centers of **Reference** for Rare Diseases (CRMR[5])
- 10 Centers of **Competencies** for Rare Diseases (CCMR[6])
- HCPs, mostly **neurologists** and **psychiatrists**

Patients

- Prevalence: **~20,000-30,000** – Incidence: **900 p.a.**
- **One national** PAG, the French Association of Narcolepsy-Cataplexy and Rare Hypersomnia (ANC[9])

Sources: French Ministry of Labor, Health and Solidarities (March 2024) – ANC and INSV websites (March 2024) – Smart Pharma Consulting analyses

[1] Agence Nationale de Sécurité du Médicament et des produits de santé – [2] Haute Autorité de Santé, via la Commission de la Transparence – [3] Comité Economique des Produits de Santé – [4] Union Nationale des Caisses d'Assurance Maladie – [5] Centre de Référence Maladies Rares – [6] Centre de Compétences Maladies Rares – [7] Indicated for pediatric Attention-Deficit/Hyperactivity Disorder, except for methylphenidate immediate-release, which is indicated for type 1 and 2 narcolepsy – [8] Also indicated for Obstructive Sleep Apnea – [9] Association Française de Narcolepsie Cataplexie et Hypersomnies Rares

The French Society of Sleep Research and Medicine promotes research and communicates guidelines to experts, while the National Institute of Sleep and Vigilance educates the public

Narcolepsy: Learned societies

CASE STUDY

French Society of Sleep Research and Medicine (SFRMS[1])

SFRMS
La Société Française de Recherche et Médecine du Sommeil

- Mission: to promote **fundamental** and **clinical research** through diverse fundings
- Members: **physicians**, other HCPs and **researchers**
- Key activities:
  - Organizes an annual Congress of Sleep
  - Communicates to experts their recommendations, guidelines and discoveries on sleeping disorders
- Part of:
  - The European Sleep Research Society (ESRS)
  - The World Association of Sleep Medicine (WASM)

National Institute of Sleep and Vigilance (INSV[2])

INSTITUT NATIONAL DU SOMMEIL ET DE LA VIGILANCE

- Mission: to ensure **prevention** and **education**
- Members: **association** of physicians and PAGs
- Key activities:
  - Communicates to authorities
  - Organizes the annual “Day of Sleep” throughout the French territory to raise awareness about sleep disorders
  - Offers an open access library of eBooks about sleep disorders, lifestyle advice, and educative supports for children and adults

Sources: National Plan of Diagnosis and Treatments (PNDS) for type 1 and 2 narcolepsy (Sept. 2021) – Respective websites – Smart Pharma Consulting analyses

[1] Société Française de Recherche et Médecine du Sommeil – [2] Institut National du Sommeil et de la Vigilance

Narcolepsy, once diagnosed, is treated in specialized centers, present throughout France, mostly by neurologists and psychiatrists

Narcolepsy: Centers of Excellence & Specialists

CASE STUDY

Hospitals & Specialists

- The French Society of Sleep Research and Medicine (SFRMS) issued approvals for **58 "Centers of Sleep"**[1] (mostly in hospitals and pluridisciplinary centers)
- Those centers can realize overnight polysomnographic recordings and evaluate patients' quality of sleep

Centers of **Reference** (CRMR[2]) & **Competencies** (CCMR[3])

- The national Center of Reference for Rare Diseases (CRMR) specialized in Narcolepsies & Rare Hypersomnia, located in Montpellier, elaborates the **National Plan** of **Diagnosis** and **Treatment** (PNDS[4]) for type 1 and type 2 narcolepsies and…
- … coordinates **16 experts centers** throughout France…
- …of which 6 of **Reference** and 10 of **Competencies**

Local HCPs (pre-diagnosis)

- Referring physician
- School nurse
- Psychologist…

Hospitals & Specialists (pre-diagnosis)

- Neurologists & neuropediatricians
- Psychiatrists & child psychiatrists

CRMR & CCMR (treatment and follow-up[4])

- Neurologists & neuropediatricians
- Psychiatrists & child psychiatrists
- Neurophysiologists
- Pulmonologists

Sources: National Plan of Diagnosis and Treatments (PNDS) for type 1 and 2 narcolepsy (Sept. 2021) – BRAIN Team website – SFMS website – Smart Pharma Consulting analyses

[1] As of March 2024 – [2] Centre de Référence Maladies Rares – [3] Centre de Compétences Maladies Rares – [4] Plan National de Diagnostic et de Soins – [5] Including treatment for comorbidities (e.g., metabolic, neuropsychiatric, sleep apnea)

There is one national PAG for narcolepsy, structured around local antennas, and complementary to associations for rare diseases

Narcolepsy: PAGs

CASE STUDY

French Association of Narcolepsy-Cataplexy and Rare Hypersomnia (ANC[1])

- **One national PAG** only, created in the national Center of Reference for Rare Diseases (CRMR[2]) of Montpellier
- The association acts through **local antennas** around **three missions**:
  - **Inform the public**, the diagnosed patients and their families on every aspect of the disease
  - **Help patients** in their lifestyle changes (e.g., work life adjustments)
  - **Promote research** of causes and solutions against the disease

Other associations

- Global, European and national associations for **rare diseases** (e.g., Rare Diseases Alliance[3] in France and Eurordis at the European level):
  - **Promote** better **information** and **diagnosis** pathways
  - **Organize meetings** for various stakeholders
  - **Contribute** to **research** through **fundraising**
- Certain Regional Health Authorities (ARS[4]) finance **regional associations**, such as the Morpheus Network[5] in the Parisian area

Sources: ANC, Alliance Maladies Rares and Réseau Morphée respective websites – Smart Pharma Consulting analyses

[1] Association Française de Narcolepsie Cataplexie et Hypersomnies Rares – [2] Centre de Référence Maladies Rares – [3] Alliance Maladies Rares – [4] Agence Régionale de Santé – [5] Réseau Morphée

Most EMA-approved drugs are CNS depressants or psychostimulants, indicated for narcolepsy with or without cataplexy, or ADHD[1] drugs used off-label

Narcolepsy: Competitors

CASE STUDY

Drug name	Sunosi	Wakix	Xyrem & Generics	Modiodal[5] & Generics	Ritalin[6] & Generics	Multiple[9]
INN	solriamfetol	pitolisant	Na oxybate (SXB)	modafinil	Methyl-phenidate	amphetamines
Mode of action	Psychostimulant	Histamine-3 receptor antagonist / inverse agonist	CNS depressant	Psychostimulant	Psychostimulant	Psychostimulant
Pharmaco-logical target	Dopamine & noradrenaline	Histamine H3	GABA-B	Dopamine & noradrenaline	Dopamine	Dopamine, noradrenaline & serotonin
Company	Pharmanovia[2]	bioprojet	UCB[4]	teva	NOVARTIS	*Multiple*
EMA approval	2020	2016	2005	~1992	~1955	~2012
Indications	Type 1 and 2 narcolepsy or OSA[3]	Type 1 and 2 narcolepsy	Type 1 narcolepsy	Type 1 and 2 narcolepsy	Type 1 and 2 narcolepsy[7] / Pediatric ADHD[8]	Pediatric ADHD[8]

Sources: HAS (March 2024) – Smart Pharma Consulting analyses

[1] Attention-Deficit/Hyperactivity Disorder – [2] In-licensing agreement with Axsome Therapeutics (Feb. 2023) – [3] Obstructive Sleep Apnea: Syndrome d'Apnées-Hypopnées Obstructives du Sommeil – [4] Licensing agreement for Europe with Jazz Pharmaceuticals (July 2008) – [5] Trade names include Provigil, Modasomil, Modalert – [6] Trade names include Concerta, Quasym, Medikinet, Rubifen – [7] Methylphenidate immediate-release has the MA for type 1 and 2 narcolepsy – [8] Used off-label for narcolepsy – [9] Including Elvanse and Vyvanse

Among the potential new entrants, the TAK-861 (Takeda) for type 1 narcolepsy, has an innovative mode of action, agonizing the orexin receptor 2, and has shown promising results in a Phase IIb

Narcolepsy: Potential new entrants

CASE STUDY

Mazindol ER[1] (Quilience) — NLS Pharmaceutics Connecting Brains

- Mode of action: CNS suppressant (dopamine & norepinephrine)
- For type 1 and type 2 narcolepsy
- Anorectic developed for obesity by Sandoz in the 60s

- POLARIS study, phase IIa completed (Jan. 2023) in the USA with 67 patients
  → Improvement of **cataplexy severity** and **EDS[2] reduction**
- **Two** ongoing **phase III** studies (AMAZE program)
  Estimated completion: January 2025

Samelisant (SUVN-G3031) — SUVEN PHARMA

- Mode of action: histamine H3 receptor inverse agonist
- For cognitive impairment in type 1 and type 2 narcolepsy, Parkinson disease, Alzheimer's disease, schizophrenia

- **Phase II completed** (Oct. 2023) in the USA and Canada with 190 patients
  → Statistically significant and clinically meaningful **EDS[2] reduction**

TAK-861 — Takeda

- Mode of action: orexin receptor 2 agonist (OX2R)
- For type 1 narcolepsy

- Phase IIb completed with 112 patients (February 2024)
  → Statistically significant and clinically meaningful at 8 weeks of **wakefulness** shown with the **Maintenance of Wakefulness Test**, of **sleepiness** shown with the **Epworth Sleepiness Scale**, of the frequency of **cataplexy** shown with the **Weekly Cataplexy Rate**
- **Phase III** trials **to be initiated** in **2024**
- No Phase III for type 2 narcoleptic patients, but ongoing research to determine a possible use of TAK-861 for other indications

Enerisant (TS-091) — TAISHO PHARMACEUTICAL

- Mode of action: histamine H3 receptor antagonist / inverse agonist
- For excessive daytime sleepiness in narcolepsy

- No optimal dose determined despite the completion of two Phase II trials (February 2022)

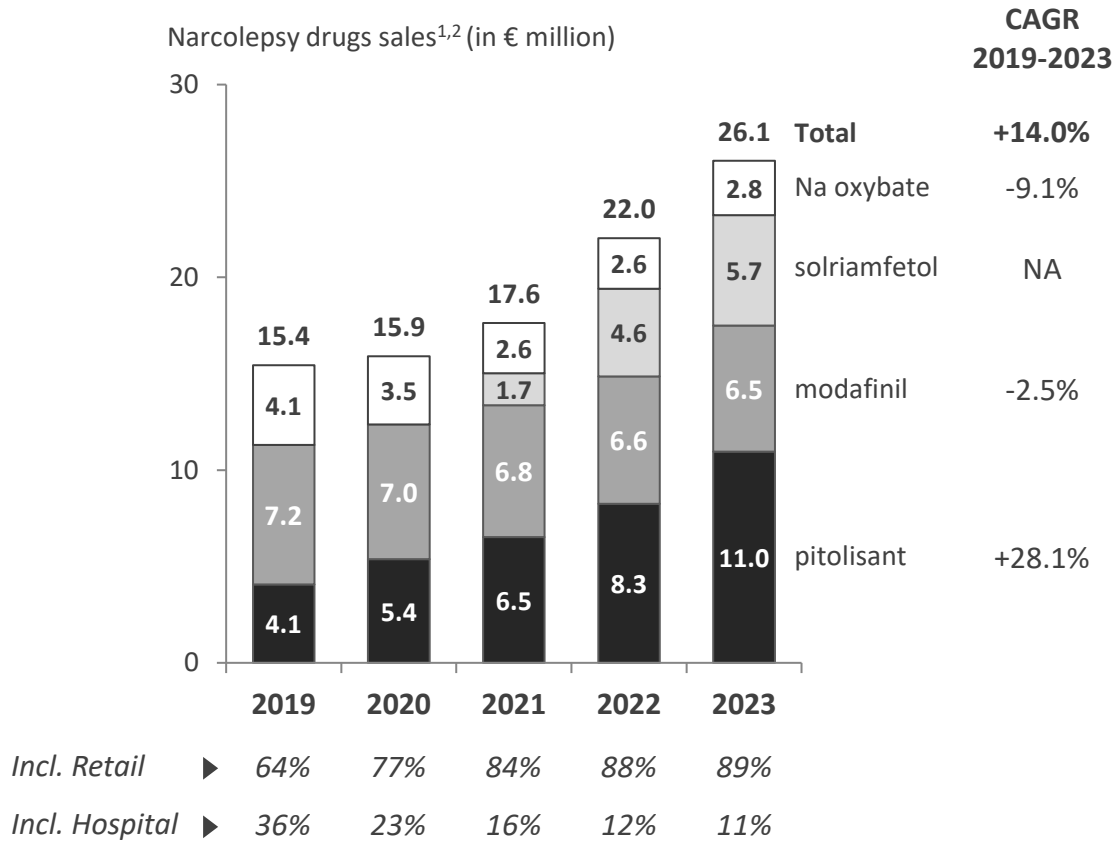
Sources: clinicaltrials.gov – Respective companies announcements – Smart Pharma Consulting analyses

[1] Extended release – [2] Excessive Daytime Sleepiness, based on the Epworth Sleepiness Scale (ESS) total score compared to placebo at day

The French narcolepsy market reached € 26 million in 2023, and its historical CAGR of +14.0% over the 2019-2023 period indicates a strong potential for new entrants

CASE STUDY

Narcolepsy: Market size – structure & dynamics (2019-2023)



	CAGR 2019-2023
Total	+14.0%
Na oxybate	-9.1%
solriamfetol	NA
modafinil	-2.5%
pitolisant	+28.1%

- The French narcolepsy market is **growing** with a **CAGR** of **+14.0%** over the 2019-2023 period
- The **retail distribution** is an increasingly important part of the total sales, with an **89% penetration rate** in 2023:
  - Na oxybate is sold only in hospitals
  - >99% of pitolisant, modafinil and solriamfetol sales are through retail distribution
- **Pitolisant** shows the highest market share (42% in 2023) and the fastest 2022-2023 growth (+32.5%)
- A certain percentage of Solriamfetol sales comes from its indication for obstructive sleep apnea

Sources: GERS (2019-2023) – Smart Pharma Consulting analyses

[1] Ex-factory sales before rebates and taxes – [2] Excluding products prescribed off-label

The success in the orphan drugs market depends on the capacity of pharma companies to develop creative and hands-on approaches focused on HCPs, patients and caregivers needs

Market challenges & implications for pharma companies

Rare disease market challenges

Each disease specificity

Implications

- Develop **in-dept market insights**:
  - What is the disease **prevalence**?
  - What is the **patient journey** (from symptoms to treatment)?
  - What **treatment centers** and type of **physicians** handle the disease?
  - Are there international or national **PAGs**[1]?
  - Is there a **patients' network**?
  - Are there any decent **sources of information** available to these patients?
  - What are the **barriers** patients might face in accessing treatment?
- Adopt a **holistic approach** by developing close relationships **with** involved **stakeholders**[2]

Under-diagnosis

Implications

- Pharma companies should help **HCPs**, **PAGs** and **patients** collect information that might be useful to characterize **typical symptoms** of the disease which is **not yet diagnosed**
- **Map** the **patient journey** to identify points in care management to educate **physicians** on their **patient profile**
- In case of low **diagnostic rate**, pharma companies could distribute **free diagnostic tests**
- Other possible **disease awareness initiatives**:
  - **Medical congresses**
  - **Forums** and **websites** to share data
  - Quality **interactions** with **medical community**
  - **Early access** programs

Strong patients' engagement

Implications

- Propose a **tailor-made approach** – around & beyond the drug – as unmet needs of **rare diseases stakeholders** are high
- **Co-create services** such as:
  - **Information** re. patients' **condition** and current **treatment options**
  - **Connection** with **KOLs** / **specialists**
  - Building of the **medical community**
  - Development of **early access programs**
- Provide **comprehensive** information and **address** the following **topics**:
  - Therapy access
  - Patients-assistance programs
  - Clinical nursing support
  - Disease education
  - Lifestyle management

Sources: "How to successfully launch a rare disease drug", McKinsey (2018) – "A nuanced message: marketing to the rare diseases community", Pharma Voice (2017) – Smart Pharma Consulting analyses

[1] Patient advocacy groups – [2] Payers, policy markers, HCPs, PAGs, patients, care givers, etc.

Pharma companies operating on the orphan drugs market in France should adopt a "start-up spirit", offer their stakeholders[1] second to none services, around and beyond their drugs

Key success factors on the orphan drugs market

Business Strategy & corresponding tactics

Market access

- Early stage interactions with **EMA** and French **health technology assessment (HTA) bodies** to agree on **clinical protocols** and **medico-economic evaluation**, respectively, are particularly important

Medical Affairs – Marketing & Sales

- **Close interactions** with academics, clinicians, PAGs and health authorities **are imperative** to be **successful** on the **rare diseases** market, so that **to join forces for earlier diagnosis** and **better** patient **management**
- Medico-marketing and sales teams should **focus** on **generating** and **disseminating data**, while **adopting** a **holistic approach** by offering specific **around / beyond** the **drug services** for HCPs and patients

Organization

- Operating on **rare diseases markets** requiring **specific skills** and a **strong engagement** with various key stakeholders …
- … it is essential for pharma companies to set up a fully dedicated organization, with a **certain degree of autonomy**[2]
- The **structure** should remain **lean** and the **processes simple**
- **Cross-functional** operating mode and **excellence** in **execution** should be a **cultural priority** to **ensure operational efficiency**

Sources: Smart Pharma Consulting analyses

[1] Payers, policy markers, HCPs, PAGs, patients, care givers, etc. – [2] Ideally for the R&D, medico-marketing and sales activities. Other functions such as regulatory and governmental affairs, market access, finance, human resources, legal affairs, etc. should be shared

Rare diseases management being a governmental priority, despite **healthcare budget constraints**, the orphan drugs market will remain attractive for companies mastering the codes of the segment

Key Takeaways: Rare diseases market in France

- Rare disease prevalence: 3 M
- Sales: € ~4.3 B in 2023[1,2]
- Sales growth: 2023 – 2028: +9.5% p.a.

- Orphan drug designation and marketing authorizations are granted by the EMA[3]…
- … and this marketing authorization is then transposed in France by the ANSM[4]
- Orphan drugs can benefit from early access authorization granted by the HAS[5]
- Direct comparators are not required for orphan drugs clinical evaluation
- Rare diseases plans have been introduced by health authorities to improve diagnosis and patient management
- 23 rare diseases healthcare networks have been set to better coordinate the actions of involved stakeholders

- Key success factors for pharma companies:
  - Establishment of early and close links with stakeholders directly concerned with the rare disease
  - Development of services to facilitate an earlier diagnosis and a better management of patients treated by orphan drugs
  - Orphan drugs should preferably be managed in fully dedicated rare disease business unit, if part of a big pharma company

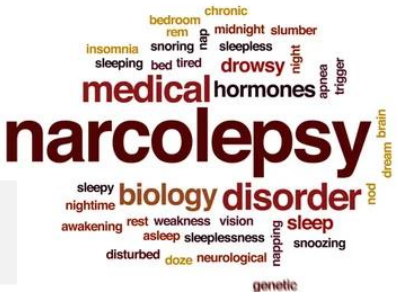
Sources: Smart Pharma Consulting analyses

[1] Ex-factory price – [2] The French orphan drug market represents 2.5% of the worldwide market – [3] European Medicines Agency – [4] Agence Nationale de Sécurité du Médicament – [5] Haute Autorité de Santé

The narcolepsy market in France is small but dynamic, and the unmet needs important, making it still attractive for newcomers with new mode of actions, such as TAK-861

Key Takeaways: Narcolepsy market in France

- Narcolepsy prevalence: 20K to 30K
- Narcolepsy incidence: 900 p.a.
- Sales: € ~26.1 M in 2023[1,2]
- Growth: 2019 – 2023: +14% p.a.
- Two learned societies: SFRMS[3] & INSV[4]
- One dedicated PAG: ANC[5]



- Disease pre-diagnosed by referring physician, school nurse, psychologists
- Disease treated by neurologists, neuro-pediatricians, psychiatrists, child psychiatrists…
- 17 expert centers for Narcolepsies and rare hypersomnia and 58 Centers of Sleep
- The drugs market is shared by 4 molecules, of which pitolisant is the leader with 42% market share in value
- Amongst the newcomers, Mazindol which is the most advanced should be followed by Samelisant and TAK-861

Sources: Smart Pharma Consulting analyses

[1] Ex-factory price – [2] The narcolepsy drug market represents 0.6% of the French orphan drug market – [3] Société Française de Recherche et Médecine du Sommeil – [4] Institut National du Sommeil et de la Vigilance – [5] Association Française de Narcolepsie Cataplexie et Hypersomnies Rares

Smart Pharma
CONSULTING

Consulting firm dedicated to the pharmaceutical sector operating
in the complementary domains of strategy, management and organization

Market Insights Series

- The Market Insights Series has in common to:
  - Be well-documented with recent facts and figures
  - Highlight key points to better understand the situations
  - Determine implications for key stakeholders
- Each issue is designed to be read in 15 to 20 minutes and not to exceed 24 pages

Rare Diseases on the French Market

Case study: Narcolepsy

In the document, Smart Pharma consultants review the rare diseases market in France and highlight the impact for pharma companies

To do so, the following topics have been covered:

- Rare diseases prevalence, management and supporting organization
- Market access conditions for orphan drugs addressing these pathologies
- Medico-market and sales challenges and KSFs for pharma companies
- Case study: Narcolepsy situation and management

Smart Pharma Consulting Editions

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  - Training activities for pharma executives
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Best regards

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