Protocol for the ongoing surveillance of the patients treated with Orphacol®

Study ORPHABASE

ORPHACOL® PATIENT SURVEILLANCE DATABASE

Version 1.1
Dated 10 January 2018
(Extracted and adapted from Orphacol® Risk Management Plan v2.2, dated 16 October 2015)

Laboratoires CTRS
63 rue de l'Est
92100 Boulogne-Billancourt
France

Signature page for the sponsor Laboratoires CTRS

Name: Virginija BAMBALAITE
Title: Associate Medical Director
Signature:

Date: 10/01/2018

Name: Philippe MARET
Title: QP-Pharmacist
Signature:

Date: 10/01/2018

CT·RS Philippe MARET Pharmacien Responsable Pharmacist - QP CNOP - N° 111.413

Name: Antoine FERRY
Title: President
Signature:

Date: 10/01/2018

Signature page for the investigator

I confirm that I have read and that I understand this protocol, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and in compliance with the Good Clinical Practice (ICH-GCP) and also protect the rights, safety, privacy, and well-being of study subjects. Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the sponsor.

Investigator's name:

Signature:

Date:

Contact Information

Sponsor contact:

Name	Title	Phone number	Email
Antoine FERRY	CEO Laboratoires CTRS	+33 1 41 220 971	aferry@ctrs.fr
Philippe MARET	Pharmacist – QP Laboratoires CTRS	+33 1 41 220 972	pmaret@ctrs.fr
Virginija BAMBALAITE	Associate Medical Director CTRS	+33 1 41 220 970	vbambalaite@ctrs.fr

Pharmacovigilance contact:

Name	Title	Phone number	Email
Pharminvent			safetyctrs@pharminvent.com
Philippe MARET	Pharmacist – QP Laboratoires CTRS	+33 1 41 220 972	pmaret@ctrs.fr

Contract Research Organization contact:

Name	Title	Phone number	Email
Céline VINCENT	Study Leader	+33 3 80 53 40 00	orphabasectrs.pala@icta.fr

Study synopsis

Study Title	Orphacol® Patient Surveillance Database
Protocol code	ORPHABASE
Name of medicinal product	Orphacol® 50 mg hard capsules Orphacol® 250 mg hard capsules The patients will be treated by the physician under his/her responsibility and as per the indications of the Orphacol® SmPC and the standard of care.
Active Pharmaceutical Ingredient (strength)	Cholic acid
Study Objectives	To increase the amount of available data on the treatment of inborn errors in primary bile acid synthesis due to 3β-HSD deficiency or Δ4-3-OxoR deficiency with Orphacol® in infants, children, adolescents and adults, and especially data on initial efficacy and safety of treatment with cholic acid.
Study design	Multi-centre, multi-national, retrospective observational study to collect patients' clinical information (treatment, safety and efficacy data) of patients receiving Orphacol® for the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (3β-HSD) deficiency or Δ^4-3-oxosteroid 5β-reductase (Δ4-3-oxoR) deficiency.
Investigators	Hospital-based Health Care Professional (HCP) managing patients of any age suffering from inborn errors in primary bile acid synthesis and treated with Orphacol®.
Conduct of the Study	Patients treated with Orphacol® will be asked for consent to participate into the database. Orphacol® is indicated for the treatment of inborn errors in primary bile acid synthesis due to 3-β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5-β-reductase deficiency in infants, children, adolescents and adults. Therefore the patients included in the patient database will include infants, children and adolescents. The parents or guardians of the paediatric patients will sign an informed consent form on behalf of the patient. A new informed consent will be obtained by the physician when paediatric patients will become adults. For the patients that consent for participation, HCP will review the medical records and will enter the following information in the database: - Demographic data for the patient - Last laboratory data available before start of treatment with cholic acid - Laboratory data right after start of treatment with cholic acid - Laboratory data available at each follow-up visit after start of treatment with cholic acid
Study Duration	This protocol will be continued as long as deemed necessary by CTRS, the regulatory authorities and the participating treating physicians.
Study Population	Patients of any age treated with Orphacol® for inborn errors in primary bile acid synthesis due to 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency.
Inclusion Criteria	All patients treated with Orphacol® and having signed an informed consent form can be included in the patient database.
Exclusion Criteria	No exclusion criteria.
Statistical methods	Inclusion of patients in the patient database is open and ongoing. It is expected that the number of inclusions will not exceed 100 patients. A patient will be followed at least once a year by the physician once the

	treatment with Orphacol® is well-established. Consequently, reports from the database will be generated for data on all patients included in the database: - at the time of PSUR preparation - and/or annually. Exploratory statistical methods may be used for analyses of the data.

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Table of abbreviations

3β-HSD	3β-hydroxy-Δ5-C27-steroid oxidoreductase
ALT	Alanine amino-transferase
AP	Alkaline phosphatase
AST	Asparate amino-transferase
CHMP	Committee for Medicinal Products for Human Use
cm	centimeters
FAB-MS	Fast Atom Bombardment/Mass Spectrometry
GC-MS	Gas Chromatography/Mass Spectrometry
GCP	Good Clinical Practices
HCP	Healthcare Professional
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
kg	kilograms
MAH	Marketing Authorisation Holder
mm	month
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Reports
QP	Qualified Person
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
yyyy	year
Δ4-3-OxoR	Δ4-3-oxosteroid 5β-reductase

Study title	Protocol status [1]	Version of protocol	Date of protocol version
Orphacol® Patient Surveillance Database	• Approved	1	03/12/2010

[1]Draft = not approved or final
Approved = when agreed by PRAC or CHMP as appropriate
Final = final version when PRAC/CHMP agreement not required

Protocol for the ongoing surveillance of the patients treated with Orphacol®: Orphacol® Patient Surveillance Database

This Patient Surveillance Database is a specific obligation of the Marketing Authorisation for Orphacol®, and its protocol is part of the current product Risk Management Plan approved by the European Medicines Agency. Data collected as part of this protocol is used as a basis for annual reassessment of the marketing authorisation and compilation of the Periodic Safety Update Reports.

1. Background Information

Cholic acid is a primary bile acid. Primary bile acids are biosynthesised in the liver of healthy mammals and are key constituents of normal bile. Cholic acid is the predominant primary bile acid in human bile.

Orphacol® (cholic acid) is indicated for the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (3β-HSD) deficiency or Δ^4-3-oxosteroid 5β-reductase (Δ^4-3-oxoR) deficiency. Both deficiencies are extremely rare genetic disorders. Due to this rarity, the available clinical data on the efficacy and safety of cholic acid in the treatment of 3β-HSD and Δ^4-3-oxoR deficiencies is more limited than for more common diseases.

The liver disease associated with 3β-HSD and Δ^4-3-oxoR deficiencies due to the production of hepatotoxic bile acid precursors is progressive and, if untreated, leads to death due to cirrhosis and liver failure, usually within the first years of life. Oral administration of cholic acid, the substance missing in an affected patient, will inhibit the production of these bile acid precursors by down-regulating cholesterol 7α-hydroxylase, the rate limiting enzyme in bile acid synthesis. In addition, it will provide a stimulus for bile flow facilitating the hepatic clearance of toxic bile acid precursors and toxic substances, including bilirubin. Furthermore, it will improve growth by facilitating the absorption of fat-soluble vitamins and fat.

The patient population includes infants and toddlers (28 days – 23 months), children (2-11 years), adolescents (12-18 years) and adults (>18 years).

Cholic acid is formulated as 50 mg and 250 mg hard capsules.

The daily dose of cholic acid is 5 to 15 mg/kg in adults and children. In adults, the daily dose should not exceed 500 mg, corresponding to the total amount of primary bile acids synthesised per day in a normal adult human. The dosage must be adjusted for each patient in a specialised unit according to blood and/or urine chromatographic bile acid profiles and liver function tests. Treatment is chronic and, in the absence of other treatment options that may arise in the future, for life.

2. Trial Objectives and Purpose

For the ongoing surveillance of patients being treated with Orphacol®, CTRS has developed a patient database. This database has two main intended functions: first, as a central tool for all Health Care Professionals (HCPs) treating patients with Orphacol® to record and access information regarding patient clinical information. In addition, CTRS will provide educational material on the diagnosis and treatment of 3β-HSD and Δ^4-3-oxoR deficiencies to Health Care Professionals through the web site that serves as portal to the patient database. Second, the database will be available to CTRS in order to have access to treatment, safety and efficacy data that can be communicated to Regulatory Authorities. Such data are in principle available from the regular (at least annual) clinical and laboratory investigations in patients, and the database will serve to capture this information in a central location. These data will be used to further increase the available safety and efficacy data and refine the therapeutic recommendations as required.

The objectives of this ongoing surveillance protocol is to increase the amount of available data on the treatment of inborn errors in primary bile acid synthesis due to 3β-HSD deficiency or Δ^4-3-OxoR deficiency with Orphacol® in infants, children, adolescents and adults, and especially data on initial efficacy and safety of treatment with cholic acid.

This protocol will be continued as long as deemed necessary by CTRS, the regulatory authorities and the participating treating physicians.

3. Selection and Withdrawal of Patients

- Inclusion criteria

All patients treated with Orphacol® and having signed an informed consent form can be included in the patient database.

- Exclusion criteria

No exclusion criteria.

- Withdrawal criteria

A patient will be withdrawn from the patient database when retracting his informed consent.

It is the treating physician's responsibility to decide if a patient should stop the treatment and document this in the database.

- Special population

Orphacol® is indicated for the treatment of inborn errors in primary bile acid synthesis due to 3-β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5-β-reductase deficiency in infants, children, adolescents and adults. Therefore the patients included in the patient database will include infants, children and adolescents.
The parents or guardians of the paediatric patients will sign an informed consent form on behalf of the patient. A new informed consent will be obtained by the physician when paediatric patients will become adults.

- Treatment of patients

The patients will be treated by the physician under his/her responsibility and as per the indications of the Orphacol® SmPC and the standard of care.

4. Data collected for each patient treated with Orphacol®

The following data will be collected in the patient database on each patient:

- Date (mm/yyyy),
- Age (precisely),
- Size, Weight,
- Deficiency: [3β HSD] or [Δ^4-3-oxoR]

Demographic and familial data:

1. Patient unique identification code (generated by the database administrator)
2. Sex
3. Date of birth (month and year only)
4. Number of siblings living (today)
5. Number of siblings who have died, and those who have probably died from the same disease
6. Number of living siblings with the same disease
7. Parental consanguinity

Diagnostic Information:

1. Date
   Age (yyyy/mm)
   Height (cm)
   Weight (kg)

2. Results:
   Fast Atom Bombardment/Mass Spectrometry (FAB-MS)
   and/or Gas Chromatography/Mass Spectrometry (GC-MS)
   or any other suitable analytical technique to detect abnormal bile acid metabolites

If available: disease gene sequence data

3. Kind of Deficiency: [3β HSD] or [Δ^4-3-oxoR]

4. Clinical Examination
   a. Icterus (jaundice)
   b. Pruritus
   c. Steatorrhoea
   d. Nausea
   e. Ascites
   f. Hepatomegaly
   g. Splenomegaly
   h. Rickets

   <u>Functional signs at diagnosis and after:</u>
   - Blood Biochemistry:
     - AST, ALT, Gamma-GT, Alkaline Phosphatase [AP]
       bilirubin (total), Serum-conjugated bilirubin
       total cholesterol, triglycerides
       Vitamin A, Vitamin D, Vitamin E, Vitamin K
       Bile Acids (total)
     - Oncological exploration: serum alpha-fetoprotein
     - Serum iron
     - 25-OH serum vitamin D
     - Cytology-Blood cell count
     - Haemostasis: fibrinogen, Quick time, Factor 11, Factor VII +X, Factor V
       Bile acids in serum
     - Primary Bile Acids: Cholic acid, Chenodeoxycholic acid
     - Secondary Bile Acids: Deoxycholic Acid, Lithocholic Acid, Ursodeoxycholic acid, total Biliary Acid, ratio Cholate/Chenodeoxycholate

   - Urinary Biochemistry
     - Creatinine
       Bile acids in urine
     - Primary Bile Acids: Cholic acid, Chenodeoxycholic acid
     - Secondary Bile Acids: Deoxycholic acid, Lithocholic acid, Ursodeoxycholic acid, Hyododeoxycholic acid, Hyocholic Acid, Total Secondary Bile Acids

   <u>Histology / Medical imaging at diagnosis and after:</u>
     - Abdominal Scan,
       Liver
       Spleen
       Hepatosplenomegaly
       Adenopathy
     - Abdominal ultrasound
       Liver
       Gallbladder
       Dilated bile ducts
       Hilum
       Spleen

Kidneys

- Cardiac Doppler
- Excrement Investigation
- Liver biopsy

Treatment and others
- Cholic acid: posology
- Associated or simultaneous treatment: drug and posology
- Other investigations or observations
- Adverse Events

Treatment
- Orphacol®: Dose/day
- Other treatment
  - In relation to the Disease
  - Without relation to the Disease

Serious Adverse Events/Reactions
- Information on SAE/SADR: event/reaction, seriousness criteria, date of occurrence, relevant tests, concomitant drugs, outcome
- Was the SAE/SADR declared to national authorities?
- Copy of the pharmacovigilance declaration submitted to the national authority

5. Assessment of Safety

5.1. Definitions

A serious adverse event/reaction (SAE/SADR) is one which:
- is fatal or life threatening,
- is permanently or significantly disabling,
- results in congenital abnormality or birth defect, or
- requires in-patient hospitalization or prolongation of hospitalization
- is assessed as serious for other medically important condition as defined by the physician.

An unexpected adverse event/reaction is one which:
- is not previously reported in the Section 4.8 of the Orphacol® SmPC, or
- is symptomatically and pathophysiologically related to a reported toxicity but differs because of greater severity or increased frequency.

5.2. Reporting

The physician is responsible for reporting to his national authorities the adverse reactions observed with Orphacol® as per the local requirements.

5.3. Collection of information

Information on the adverse events/reactions to Orphacol® is collected in the patient database. The SAE/SADR should be reported in the Serious Adverse Events/Reactions section of the patient database.

The following information is requested:

- Information on SAE/SADR: event/reaction, seriousness criteria, date of occurrence, relevant tests, concomitant drugs, outcome
- Was the SAE/SADR declared to national authorities?
- Copy of the pharmacovigilance declaration submitted to the national authority

A warning system will inform CTRS of the posting of any SAE/SADR information in the safety database. This information will be immediately retrieved by CTRS for regular pharmacovigilance data processing, as per current processes in place.

6. Statistics

Inclusion of patients in the patient database is open and ongoing. It is expected that the number of inclusions will not exceed 100 patients.
A patient will be followed at least once a year by the physician once the treatment with Orphacol® is well-established. Consequently reports from the database will be generated for data on all patients included in the database:

- at the time of PSUR preparation
- and/or annually.

Exploratory statistical methods may be used for analyses of the data.

7. Direct Access to Source Data/Documents

Source data will be recorded by a HCP under the treating physican's responsibility.

8. Quality Control and Quality Assurance

Data are entered by a HCP or delegated person under the treating physican's responsibility. The data will be reviewed for consistency at least once per year by CTRS before definite inclusion into the database, as per the CTRS Quality Assurance procedures. Potential data queries will be resolved in direct interaction with the reporting HCP.

9. Ethical consideration

The consent of the patient or his or her parent or guardian to the collection of the above defined medical data will be obtained and filed by the treating physician. CTRS will systematically request a proof of signature of the informed consent (acknowledgment from the physician that the ICF has been signed), as per current internal processes.

The proof of signature of a new informed consent will be requested by CTRS when paediatric patients will become adults.

The national requirements in every country where a patient will be treated will be clarified in detail and on a case by case basis as patients are identified. For patients treated in France, the French Commission Nationale de l'Informatique et des Libertés (National informatics and civil liberties commission; CNIL) has been notified regarding the patient database (declaration number: 1210041).

10. Data Handling and Record Keeping

Data are entered by a HCP or delegated person under the treating physican's responsibility. The physician will keep record of any source data and of the subject's medical documentation.

The data collected from the 19 currently treated patients under compassionate use have been retrospectively imported in the patient database, unless their consent was withdrawn.

10.1. Database description

A simple database was chosen by CTRS as the approach to data collection that addresses best the requirement for collection of particularly safety data in an extended patient population. A more formalised approach, for example a patient registry or an observational study, would introduce an excessive financial and administrative burden for this very small patient population, and for CTRS as a Small Enterprise.

The database is set up in a way that treating health care professionals can enter treatment and safety information on their patients. Such data are available at every examination of a patient during establishment of the diagnosis, titration of the appropriate cholic acid dose, and during the regular follow-up investigations. The database serves to capture this information, for the reference of the health care professional and for analysis by CTRS and Regulatory Authorities.

CTRS controls and maintains the database. The database will use internationally recognized programmes like Access or Excel.

The flow chart depicted in Figure 1, sets out how authorized persons are able to access:

1. general information regarding inborn errors of primary bile acid synthesis;
2. pharmacovigilance information and
3. clinical information regarding patient sets being treated with Orphacol®.

Access to the database is set up as a tier system, whereby entry into the database is identification (ID) and password sensitive.

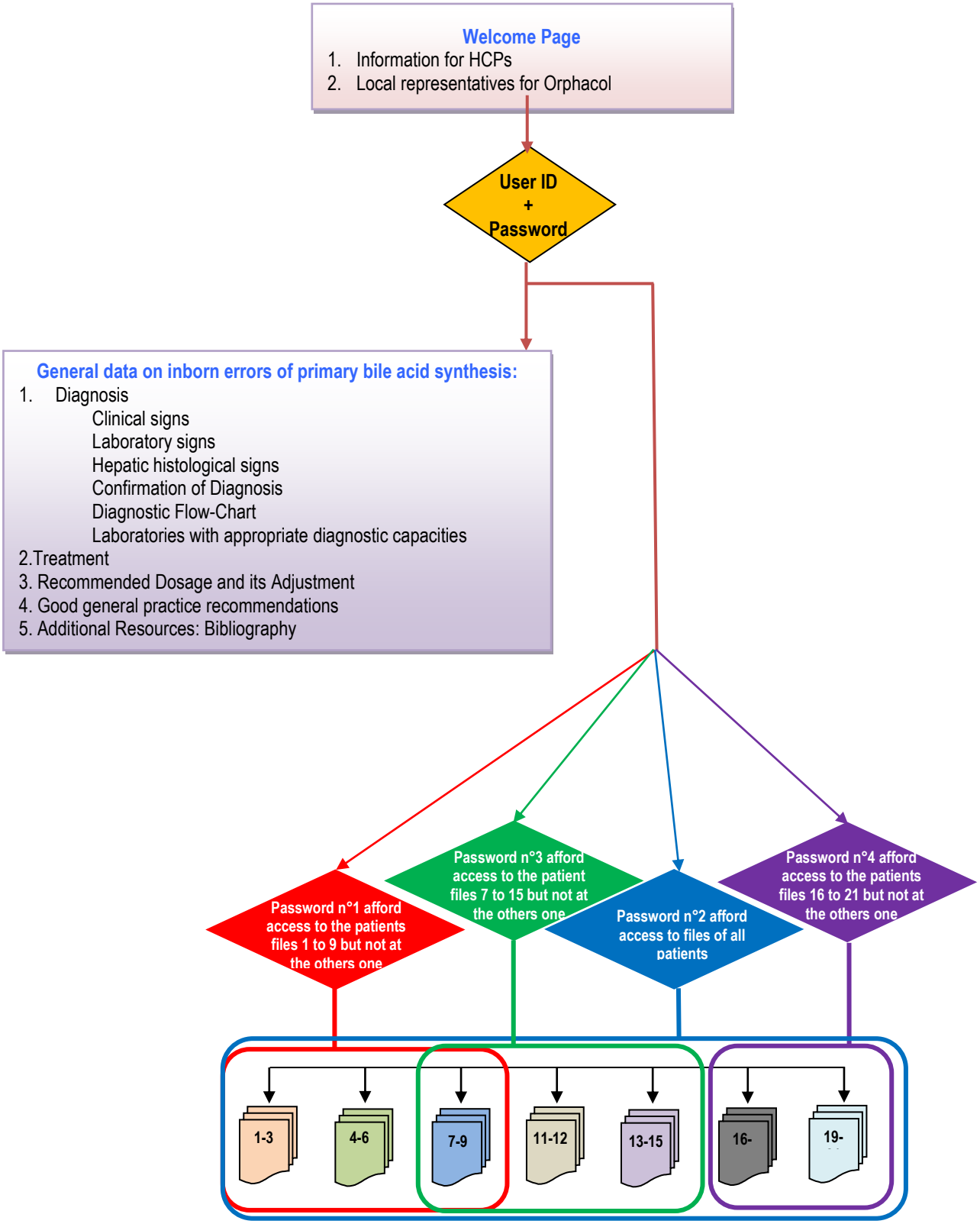
Health Care Professionals may request access to the database by their own initiative, or after having been contacted by CTRS. Additionally, as few laboratories have the analytical capacities for the analyses of serum and urine bile acid metabolites required for diagnosis, CTRS will establish and/or maintain close contact to these laboratories in order to ensure that HCPs are systematically informed about the availability of the patient database resource.

As shown in Figure 1 of the protocol, there is an access control to the Orphacol® Patient Surveillance Database. A first access to a welcome web page is open to all visitors and contains high-level information on inborn errors of bile acid synthesis destined to HCPs.

In order to gain access to the restricted level General data on inborn errors of primary bile acid synthesis, users need to request a user ID and password from the MAH. This access control is intended to ensure that only properly qualified HCPs have access to this information, as required legally in a number of Member States.

The web site is non-promotional and open for inspection by Regulatory Authorities for adherence to this requirement.

Figure 1: Flow chart for accessing the patient database



10.2. Controlled access level

Below are the instructions on how a health professional will enter the patient database and Orphacol® Educational website and Patient Database and what information will be available for him/her at this level of access. The aim of this level of access is to disseminate information to physicians and other HCPs that will help them to correctly identify and initially treat patients with 3β-HSD deficiency or Δ^4-3-oxoR deficiency.

1. Access the web site via the electronic address
www.databaseorphacol.com/
Documentation on Orphacol® providing information on the possibility to access the website will be distributed to the EU Reference Centres for the disease.

2. Enter your User ID and your Password
User ID: **1234567890**
Password: **C2TOROS9**
The password will be granted by CTRS upon receipt of a request by email. The requestor will have to provide CTRS with a statement confirming that he/she is a health care professional.

3. Available information (content may change according to local requirements)

I. General data on:
Inborn errors of primary bile acid synthesis

II. Diagnosis
   a. Clinical signs
   b. Laboratory signs
   c. Hepatic histological signs
   d. Confirmation of Diagnosis
   e. Diagnostic Flow-Chart
   f. Laboratories with appropriate diagnostic capacities

III. Treatment
   a. Restoration of the bile acid-dependent component of bile flow
   b. Inhibition of the production of hepatotoxic and cholestatic primary bile acid precursors
   c. Improvement of the child's growth

IV. Recommended dosage of cholic acid to treat *3β-hydroxy-*Δ^5*-*C_{27}*-steroid dehydrogenase/isomerase* and Δ^4*-3-oxosteroid-5β-reductase* deficiencies

V. Good general practice recommendations for patients with 3β-HSD deficiency or Δ^4-3-oxoR deficiency, including appropriate measures to prevent hepatic impairment, such as a healthy diet and low alcohol intake, vaccination against hepatitis, and avoidance of hepatotoxic xenobiotics, including medicinal products.

VI. Additional Resources

a. Link to the Orphacol EPAR and product information on the Agency's web site
b. Bibliography

All educational material on this web site will be prepared in accordance with the approved product information, national competent authority requirements, and monitored by CTRS's Scientific Service. Approved educational material are available in PDF format for the countries where they are approved by local authorities.

4. Patient database

In this patient database section, HCPs will be able to view their patients' information including demographics and family history, diagnostics, treatment and adverse events, as well as adding new patient.

HCPs have access to a data entry interface that will enable them to enter the data listed above (see section 4) as they are generated during the treatment of their patients.
Data that have been entered will be reviewed for consistency by CTRS before definite inclusion into the database. Potential data queries will be resolved in direct interaction with the reporting physician.

10.3. Monitoring

The database will be monitored for effectiveness by the following measures:

- Due to the low number of patients, treatment centres and hence treating physicians, CTRS will be aware of most or even all physicians that are treating patients with 3β-HSD deficiency or Δ^4-3-oxoR deficiency. It will therefore be possible to link commercial information with the registration of HCPs with the web site, and to take contact individually with HCPs to motivate them to participate in the data collection effort.

- A patient will be followed at least once a year by the treating physician once the treatment with Orphacol® is well-established. Therefore, CTRS can monitor whether the information for any given patient has been updated in the corresponding time span, and therefore again stimulate data entry by HCPs.

- Data are entered by the HCP or delegated person under the respective treating physician's responsibility. The data will be reviewed for consistency at least once per year by CTRS before definite inclusion into the database, as per the CTRS Quality Assurance procedures. Potential data queries will be resolved in direct interaction with the reporting HCP.

11. Financing and Insurance

The financial responsibility for maintaining the database lies with CTRS.

12. Publication Policy

HCPs are free to use any data that have been included by themselves in the database for their own publications. CTRS does not claim first publishing rights.

Any publications derived from the data included in the database will be communicated to the regulatory authorities.