オファコルカプセル 50 mg
に関する資料

第 1 部：申請書等行政情報及び添付文書
に関する情報

1.6　外国における使用状況等に関する資料

本資料に記載された情報に係る権利及び内容の責任は、株式会社レクメドに帰属するものであります。当該情報を適正使用以外の営利目的に本資料を利用することはできません。

株式会社レクメド

目次

1.6 外国における使用状況等に関する資料.....3
1.6.1 外国での承認（許可）及び使用状況.....3
1.6.2 代表的な添付文書.....3

図表目次

表 1.6-1 オファコルの世界各国での製造販売承認状況及び販売状況.....3

1.6　外国における使用状況等に関する資料

1.6.1　外国での承認（許可）及び使用状況

オファコルの世界各国での製造販売承認状況及び販売状況を表 1.6-1 に示す。

表 1.6-1 オファコルの世界各国での製造販売承認状況及び販売状況

国	製剤	承認取得日	医薬品販売承認番号	発売日
EU 加盟国				
EU 各国 a)	Orphacol 50 mg、硬カプセル剤 a,b	2013 年 9 月 12 日	EU/1/13/870/001	[redacted]
	Orphacol 250 mg、硬カプセル剤		EU/1/13/870/004	
EU 加盟国以外				
アルゼンチン	Orphacol 50 mg、硬カプセル剤 30 個、60 個、120 個入	2019 年 5 月 17 日	1-0047-0000-014024-17-6	[redacted]
	Orphacol 250 mg、硬カプセル剤 30 個、60 個、120 個入			
コロンビア b)	Orphacol 50 mg、硬カプセル剤 30 個入	2019 年 8 月 15 日	2019M-0019109	[redacted]
アラブ首長国連邦	Orphacol 50 mg、硬カプセル剤 30 個	2021 年 1 月 18 日	49198-1561-61650	[redacted]
	Orphacol 250 mg、硬カプセル剤 30 個		49198-1561-61644	
アルジェリア	Orphacol 50 mg、硬カプセル剤 30 個入	2021 年 7 月 11 日	21/14 N 388/242	[redacted]
	Orphacol 250 mg、硬カプセル剤 30 個入		21/14 N 389/242	
英国	Orphacol 50 mg、硬カプセル剤	2013 年 9 月 12 日 c)	PL 44776/0003	[redacted]
	Orphacol 250 mg、硬カプセル剤		PL 44776/0002	

a) Orphacol is commercialised in [redacted] and [redacted] based on a special agreement for treatment reimbursement without a formal commercialisation declaration (in [redacted] on a “named-patient basis for reimbursement”).

b) Despite receiving the marketing authorisation for Orphacol 50 mg, 30 hard capsules in Colombia on 15 August 2019, the product was still supplied through named patient programme until [redacted].

c) The marketing authorisation for the UK was automatically authorised after BREXIT on 01 January 2021; this was previously approved under the centralised EU procedure, initially granted on 12 September 2013.

1.6.2　代表的な添付文書

代表的な添付文書として、欧州における本剤の添付文書（最終更新日：2022 年 6 月 23 日）を添付する。

▼本剤は追加モニタリングの対象品目である。これにより、新たな安全性情報を速やかに把握することができる。医療従事者は、あらゆる疑わしい副作用を報告することが求められる。副作用の報告方法については第4.8項を参照のこと。

1. 医薬品名

Orphacol 50 mg硬カプセル
Orphacol 250 mg硬カプセル

2. 定性的及び定量的組成

Orphacol 50 mgカプセル
1カプセル中にコール酸50 mgを含有する。

Orphacol 250 mgカプセル
1カプセル中にコール酸250 mgを含有する。

既知の作用を有する賦形剤：ラクトース一水和物（50 mgカプセル中145.79 mg、250 mgカプセル中66.98 mg）

全賦形剤の一覧については、第6.1項を参照のこと。

3. 剤型

硬カプセル（カプセル）

Orphacol 50 mgカプセル
楕円形の不透明な青色及び白色のカプセル

Orphacol 250 mgカプセル
楕円形の不透明な緑色及び白色のカプセル

4. 臨床に関する項目

4.1 効能・効果

Orphacolは、1カ月から18才の乳児、小児、青年及び成人における3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症又はΔ^4-3-Oxosteroid-5β-reductase欠損症による一次胆汁酸合成の先天性胆汁酸代謝異常症の治療を適応とする。

4.2 用法・用量

治療は経験豊富な消化器専門医/肝臓専門医、小児患者の場合は小児消化器専門医/肝臓専門医によって開始及び観察すること。

コール酸単剤療法に対する治療効果が持続して得られない場合、他の治療を考慮すること（第4.4項参照）。患者のモニタリングは以下のように行うこと；投与開始初年は3カ月毎、その後3年間は6カ月毎、それ以降は1年毎（以下を参照）。

用量
血液及び/又は尿クロマトグラフィーによる胆汁酸プロファイルに従って、専門部署が各患者の用量を調整する必要がある。

- 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症

幼児、小児、青年及び成人における1日量は5～15 mg/kgである。すべての年齢において、最小用量は50 mgとし、用量は50 mgずつ調整すること。成人の1日用量は500 mgを超えないこと。

- Δ^4-3-oxosteroid-5β-reductase欠損症

幼児、小児、青年及び成人における1日量は5～15 mg/kgである。すべての年齢において、最小用量は50 mgとし、用量は50 mgずつ調整すること。成人の1日用量は500 mgを超えないこと。

1日量が複数のカプセルになる場合、体内でのコール酸の持続的産生を模倣すること及び1回当たりの服用カプセル数を減らすことを目的として1日量を分割して投与してもよい。

治療開始及び用量調整時には、適切な分析手法を用いて、血清及び/又は尿中の胆汁酸レベルを集中的に観察する必要がある（少なくとも治療開始1年目は3カ月毎、2年目は6カ月毎）。3β-Hydroxy-Δ5-C27-steroid oxidoreductase欠損症（3β, 7α-dihydroxy- and 3β, 7α, 12α-trihydroxy-5- cholenoic acids）又はΔ^4-3-Oxosteroid-5β-reductase欠損症（3-oxo-7α-hydroxy- and 3-oxo-7α, 12α-dihydroxy-4-cholenoic acids）で合成された異常な胆汁酸代謝産物の濃度を確認する必要がある。各検査では、投与量を調整する必要性について考慮すること。異常な胆汁酸代謝産物を可能な限りゼロまで減少させるコール酸の最低用量を選択する必要がある。

過去に他の胆汁酸又は他のコール酸製剤で治療された患者は、Orphacolによる治療の開始時に同様に検査する必要がある。上記のとおり、検査結果に応じ用量を調整すること。

肝機能パラメータについて、血清及び/又は尿中の胆汁酸レベルよりも頻度高く優先的に検査する必要がある。血清ガンマグルタミルトランスフェラーゼ（GGT）、アラニンアミノトランスフェラーゼ（ALT）及び/又は血清胆汁酸が同時に基準値を超える上昇を示す場合は、コール酸の過量投与の可能性がある。コール酸治療の開始時にトランスアミナーゼの一過性の上昇が観察されており、GGTが上昇せず、血清胆汁酸濃度が減少又は基準値範囲内にあれば減量の必要性がないことを示唆している。

導入期間後は、（適切な分析手法を使用して）血清及び/又は尿中の胆汁酸と肝機能検査値を確認し投与量を少なくとも毎年調整する必要がある。急速な成長、合併症及び妊娠期間中には治療をモニタリングするために、追加検査若しくはより頻回に検査を行う必要がある（第4.6項参照）。

特別な集団
- 高齢者（65歳以上）

高齢者の使用経験はない。コール酸の投与量は個別に調整すること。

- 腎機能障害

腎機能障害患者に関するデータはない。コール酸の投与量は個別に調整すること。

- 肝機能障害

3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症又はΔ^4-3-Oxosteroid-5β-reductase欠損症による軽度から重度の肝障害を有する患者の限られた報告がある。患者は、診断時にある程度の肝障害を呈することが予想され、その肝障害はコール酸治療下で改善される。コール酸の投与量は個別に調整すること。

3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症又はΔ^4-3-Oxosteroid-5β-reductase欠損症以外の原因による肝障害の患者での使用経験はなく、投与推奨もない。肝障害のある患者は注意深く監視する必要があ

る（第4.4項参照）。

● 家族性高トリグリセリド血症

家族性高トリグリセリド血症の新規発症患者又は家族歴を有する患者は、腸管におけるコール酸の吸収が不良であると考えられる。家族性高トリグリセリド血症の患者でのコール酸の投与量は、記載したように用量を設定及び調整する必要があるが、特に成人患者での1日用量の上限である500 mgを超える用量が必要となる場合があり、そのような用量でも安全であると考えられる。

● 小児集団

コール酸は、生後1カ月の乳児から小児及び青年に使用されている。推奨用量は、この集団での使用経験を反映している。生後1カ月から2歳までの乳児、小児及び青年の1日用量は5～15 mg/kgの範囲であり、個別の患者ごとに調整すること。

投与方法

Orphacolカプセルは、朝及び/又は夕方の毎日ほぼ同じ時間に食物と一緒に服用する必要がある。食物と一緒に投与すると、コール酸のバイオアベイラビリティが向上し、忍容性が向上する可能性がある。投与を規則的に時間を定めて実施することにより、患者又は介護者のコンプライアンスの一助となる。カプセルは噛まずに水で完全に飲み込むこと。

カプセルを服用できない乳児及び小児では、カプセルを開けて、内容物を乳児用調合乳又はジュースに追加することができる。その他の情報については第6.6項を参照のこと。

4.3 禁忌

本剤の有効成分又は第6.1項に示した賦形剤に対して過敏症のある患者

フェノバルビタール及びプリミドンのコール酸との併用（第4.5項参照）

4.4 警告及び使用上の注意

コール酸の使用により、致死症例を含む重度の肝毒性症例が報告されている。肝機能障害のある患者にコール酸を投与する場合には慎重な監視下で行い、すべての患者において、3カ月以内にプロトロンビン時間で確認される肝機能異常が改善しない場合、コール酸による治療を中止すること。尿中総胆汁酸量が同時に減少していることも観察すること。重度の肝不全の明確な徴候が認められる場合は、早期に治療を中止すること。

家族性高トリグリセリド血症

家族性高トリグリセリド血症と診断された患者又は家族歴のある患者では、コール酸の腸内吸収が不十分になると予想される。家族性高トリグリセリド血症の患者でのコール酸の投与量は、記載したように用量を設定及び調整する必要があるが、特に成人患者での1日用量の上限である500 mgを超える用量が必要となる場合がある。

賦形剤

Orphacolカプセルは乳糖を含有する。ガラクトース不耐性、ラップラクターゼ欠損症又はグルコース－ガラクトース吸収不全症の遺伝性希少疾患を有する患者は、本剤を服用しないこと。

4.5 他の医薬品との相互作用及びその他の相互作用

フェノバルビタール及びプリミドン（部分的にフェノバルビタールに代謝される）はコール酸の効果に対する拮抗作用がある。コール酸で治療している3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症又はΔ^4-3-Oxosteroid-5β-reductase欠損症の患者へのフェノバルビタール及びプリミドンの使用は禁忌である（第4.3項参照）。代替治療を使用すること。

シクロスポリンは、胆汁酸の肝臓取り込み及び肝胆汁分泌を阻害することでコール酸の薬物動態を変化させ、cholesterol 7α-hydroxylaseの阻害によりその薬力学を変化させる。シクロスポリンとの併用は避けること。シクロスポリン投与が必須と考えられる場合、血清及び尿中の胆汁酸濃度を綿密に監視し、その結果に応じてコール酸の用量を調整する必要がある。

胆汁酸封鎖剤（コレスチラミン、コレスチポール、コレセベラム）及び特定の制酸剤（水酸化アルミニウム等）は胆汁酸と結合し、胆汁酸を排泄する。これらの医薬品の投与により、コール酸の効果が低下する可能性がある。胆汁酸封鎖剤又は制酸剤の投与時は、医薬品が最初に投与されるかにかかわらず、コール酸と他の医薬品の投与に5時間の間隔をあけること。

ウルソデオキシコール酸は、コール酸を含む他の胆汁酸の吸収を競合的に阻害する。また、腸肝循環内で胆汁酸を置換し、経口投与したコール酸による胆汁酸合成の負のフィードバック制御を抑制する。ウルソデオキシコール酸とコール酸をそれぞれ単回ずつ投与する際は、両薬剤の投与間隔を空ける。一方を朝に投与した場合は他方を夕に投与する。投与の順序は問わない。それぞれ又はどちらかを複数回投与する場合は、ウルソデオキシコール酸とコール酸との投与間隔を数時間あけること。

コール酸のバイオアベイラビリティに対する食物の影響は検討されていない。食物とともに投与すると、理論上ではコール酸のバイオアベイラビリティが向上し、忍容性が向上する可能性がある。

4.6　妊孕性、妊娠及び授乳

<u>妊娠可能な女性</u>
コール酸で治療された妊娠可能な女性又はそのパートナーでは避妊の必要はない。妊娠可能な女性で妊娠が疑われた場合は、速やかに妊娠検査をすること。

<u>妊娠</u>
妊婦から得られたコール酸の使用に関するデータは限られている（妊娠転帰は20件未満）。妊娠中のコール酸の曝露では副作用を示さず、正常で健康な子供を出産した。動物実験では、生殖毒性に関して直接的又は間接的な有害な影響は示されていない（第5.3項参照）。

妊娠中の女性は、治療を継続することが極めて重要である。予防措置として、妊婦及び胎児を綿密に観察すること。

<u>授乳</u>
コール酸及びその代謝物は乳汁に移行するが、Orphacolは治療用量では母乳で育てた新生児/乳児への影響は小さいと予想される。授乳中もOrphacolの使用は可能である。

<u>妊孕性</u>
コール酸の妊孕性への影響に関するデータはない。治療用量では、妊孕性への影響はないと予想される。

4.7　運転及び機械操作能力に与える影響

コール酸は、運転及び機械操作能力に影響を与えない、若しくは、無視できる程度の影響しか与えない。

4.8　副作用

<u>安全性プロファイルの要約</u>

疾患の希少性により、最も重篤及び/又は最も頻度の高い副作用に関する情報は少ない。過量投与を原因として下痢、トランスアミナーゼ上昇及びそう痒症が報告されており、減量により消失した。ごく少数例で長期投与を原因とする胆石形成が報告されている。

副作用の一覧表
コール酸治療中の文献で報告された副作用を示した。これらの頻度は不明である（入手可能なデータでは推定できなかった）。

MedDRA器官別大分類	副作用
胃腸障害	下痢
肝胆道系障害	トランスアミナーゼ上昇 胆石
皮膚および皮下組織障害	そう痒症

主な副作用の説明
そう痒症及び/又は下痢の発生は、Orphacolによる治療中に観察された。これらの反応は減量後に軽減したことから、過量投与が示唆される。そう痒症及び/又は持続性の下痢を呈する患者は、血清及び/又は尿胆汁酸の検査により過量投与の可能性に留意すること（第4.9項参照）。

また、長期治療後に胆石が報告されている。

小児集団
提示した安全性情報は主に小児患者から得られたものである。十分な量の文献がないため、小児の年齢層内又は小児患者と成人間のコール酸の安全性の差を明らかにすることはできない。

その他の特別な集団
特別な集団におけるOrphacolの使用については、第4.2項を参照のこと。

疑わしい副作用の報告
本剤承認後にみられた疑わしい副作用の報告は重要である。これにより、本剤のベネフィットリスクバランスを継続的にモニタリングすることができる。医療関係者は、the national reporting system listed in Appendix Vを通じてあらゆる疑わしい副作用を報告することが求められる。

4.9 過量投与

偶発的な過量投与を含む症候性の過量投与の事例が報告されている。臨床的な徴候はそう痒症と下痢のみであった。臨床検査では、GGT、トランスアミナーゼ及び血清胆汁酸濃度の上昇が認められた。投与量の減量により、臨床症状と臨床検査値の異常は是正される。

偶発的な過量投与の場合、臨床的な徴候及び/又は生物学的な異常の回復後、推奨用量で治療を継続すること。

5. 薬理学的特性

5.1 薬力学的特性

薬効分類：胆汁及び肝治療、胆汁酸及び誘導体、ATCコード：A05AA03

コール酸は、ヒトの主要な一次胆汁酸である。3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductaseやΔ^4-3-Oxosteroid-5β-reductaseの先天性欠損患者では、一次胆汁酸の生合成が減少又は欠如している。先天性胆汁酸代謝異常症のいずれの病型も極めて稀な遺伝性疾患であり、欧州では、人口1,000万人あた

り3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症の患者が約3～5人であり、Δ^4-3-Oxosteroid-5β-reductase欠損症の有病率は10倍低いと推定される。治療が行われない状態では、非生理学的な胆汁うっ滞及び肝毒性のある胆汁酸代謝物が、肝臓、血清、尿中に増加する。コール酸治療により、胆汁流の胆汁酸依存性の構成成分が回復、胆汁分泌の回復及び毒性代謝産物の胆汁による除去が可能になり（胆汁酸合成の律速酵素であるcholesterol 7α-hydroxylaseに対する負のフィードバックによる毒性胆汁酸代謝産物の産生の抑制）、脂肪及び脂溶性ビタミンの腸管吸収不良が改善されることにより、患者の栄養状態を改善する。

文献では、小規模の患者コホート及び単一症例報告からの臨床使用経験が報告されている。しかし、疾患の希少性により患者の絶対数は少ない。この希少性により、対照群を置く臨床試験の実施は不可能であった。全体として、3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase欠損症の患者約60名のコール酸治療の結果が報告された。コール酸単剤療法による治療に関する詳細な長期データとしては、最長12.9年間観察された14名の患者情報が入手可能である。また、Δ^4-3-Oxosteroid-5β-reductase欠損症患者7名の最大14年間のコール酸治療の結果が報告されており、5名について詳細な中長期データが利用可能である。そのうち1名はコール酸単独療法で治療されていた。経口コール酸療法から、肝移植の必要性を延期又は回避できること、臨床検査パラメータを改善すること、肝臓の組織学的病変を回復し、患者のすべての症状を大幅に改善することが示されている。コール酸療法中の尿の質量分析では、コール酸の存在と、毒性のある胆汁酸代謝産物の著しい減少又は完全な消失を示す。これは、胆汁酸合成と代謝平衡における効果的なフィードバック制御の回復を反映している。さらに、血中コール酸濃度は正常で、脂溶性ビタミンは正常範囲に回復した。

小児集団
文献に報告されている臨床使用経験は、3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase及びΔ^4-3-Oxosteroid-5β-reductaseの先天性欠損の生後1箇月の乳児を含む、主に小児及び青年の患者集団からのものである。ただし、報告の絶対数は少ない。

本剤は、「例外的状況下」で承認されている。
これは、疾患の希少性及び倫理的な理由により、本剤に関する完全な情報を収集することが不可能であることを意味している。
欧州医薬品庁は、毎年得られる新たな情報を審査し、必要に応じて本製品概要（SmPC）を改訂する予定である。

5.2 薬物動態特性

一次胆汁酸であるコール酸は、回腸で部分的に吸収される。未吸収の胆汁酸は、腸内細菌による7α-ヒドロキシ基の還元によりデオキシコール酸（3α, 12α-dihydroxy）へ変換される。
デオキシコール酸は二次胆汁酸である。一次及び二次胆汁酸の90%超は、特定の能動輸送体によって回腸で再吸収され、門脈を通じて肝臓に還元され、残りは糞便中に排泄、胆汁酸のごく一部が尿中に排泄される。

Orphacolの薬物動態試験に関するデータはない。

5.3 非臨床安全性データ

文献の入手可能な非臨床データでは、安全性薬理、反復投与毒性、遺伝毒性、がん原性、生殖毒性の研究に基づいて、ヒトに特別な危険性はないことを明らかにしている。しかし、コール酸は動物及びヒトの生理的物質であることから、医薬品と同程度の詳細まで研究は実施されていない。

コール酸のマウス静脈内LD_{50}は350 mg/kgであった。非経口投与では溶血及び心停止を引き起こす可能性がある。経口投与の場合、胆汁酸及び胆汁酸塩の毒性は通常ごく軽微である。マウス経口LD_{50}

は1520 mg/kgであった。コール酸の反復投与試験で報告頻度の高い事象は、体重減少、下痢及びトランスアミナーゼの上昇を伴う肝臓障害であった。コール酸とコレステロールを併用投与した反復投与試験では、肝臓重量の増加と胆石が報告されている。

In vitroで実施されたコール酸の一連の遺伝毒性試験では、有意な変異原性活性を示さなかった。動物実験では、コール酸は催奇形性や胎児毒性を誘発しないことが示されている。

6. 製剤に関する項目

6.1 賦形剤一覧

カプセル内容物：
ラクトース一水和物、
軽質無水ケイ酸、
ステアリン酸マグネシウム

カプセル外殻 Orphacol 50 mgカプセル：
ゼラチン（ウシ由来）、
二酸化チタン（E171）、
青色2号（E132）

カプセル外殻 Orphacol 250 mgカプセル：
ゼラチン（ウシ由来）、
二酸化チタン（E171）、
青色2号（E132）
黄酸化鉄（E172）

6.2 配合禁忌

該当せず。

6.3 有効期間

3年

6.4 保存上の特別な注意

30°C未満で保存すること。

6.5 容器の性質及び内容

PVC/PVDC-アルミニウムブリスター（10カプセル入り）
パックサイズ：30、60及び120カプセル
必ずしも上記の全サイズが市販されているわけではない。

6.6 廃棄及びその他の処理上の特別な注意

- 小児集団への投与

第4.2項も参照のこと。カプセルを服用できない乳児及び小児では、カプセルを開けて、内容物を乳児用調合乳、乳幼児用リンゴ/オレンジジュース又はリンゴ/アプリコットジュースに加えて服用

してもよい。フルーツコンポートやヨーグルト等のその他の食物は投与に適していると考えられるが、適合性又は嗜好性に関するデータは得られていない。

未使用の製品又は廃棄物は各国の要件に従って廃棄すること。

7. 医薬品販売承認取得者

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

8. 医薬品販売承認番号

カプセル外殻 Orphacol 50 mgカプセル：
EU/1/13/870/001
EU/1/13/870/002
EU/1/13/870/003

カプセル外殻 Orphacol 250 mgカプセル：
EU/1/13/870/004
EU/1/13/870/005
EU/1/13/870/006

9. 初回承認日/承認更新日

初回承認日：2013年9月12日
最新更新日：2019年4月24日

10. 本文改訂日

詳細な情報は、欧州医薬品庁のウェブサイトhttp://www.ema.europa.euに掲載されている。

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Orphacol 50 mg hard capsules
Orphacol 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Orphacol 50 mg capsules
Each hard capsule contains 50 mg of cholic acid.

Orphacol 250 mg capsules
Each hard capsule contains 250 mg of cholic acid.

Excipient(s) with known effect: Lactose monohydrate (145.79 mg per capsule of 50 mg and 66.98 mg per capsule of 250 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Orphacol 50 mg capsules
Oblong, opaque, blue and white capsule.

Orphacol 250 mg capsules
Oblong, opaque, green and white capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orphacol is indicated for the treatment of 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 in infants, children and adolescents aged 1 month to 18 years and adults.

4.2 Posology and method of administration

Treatment must be initiated and monitored by an experienced gastroenterologist/hepatologist or a paediatric gastroenterologist/hepatologist in the case of paediatric patients.

In case of persistent lack of therapeutic response to cholic acid monotherapy, other treatment options should be considered (see section 4.4). Patients should be monitored as follows: 3-monthly during the first year, 6-monthly during the subsequent three years and annually thereafter (see below).

Posology

The dose must be adjusted for each patient in a specialised unit according to blood and/or urine chromatographic bile acid profiles.

3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency

The daily dose ranges from 5 to 15 mg/kg in infants, children, adolescents and adults. In all age groups, the minimum dose is 50 mg and the dose is adjusted in 50 mg steps. In adults, the daily dose should not exceed 500 mg.

Δ^4-3-Oxosteroid-5β-reductase deficiency

The daily dose ranges from 5 to 15 mg/kg in infants, children, adolescents and adults. In all age groups, the minimum dose is 50 mg and the dose is adjusted in 50 mg steps. In adults, the daily dose should not exceed 500 mg.

The daily dose may be divided if it consists of more than one capsule in order to mimic the continuous production of cholic acid in the body and to reduce the number of capsules that need to be taken per administration.

During the initiation of therapy and dose adjustment, serum and/or urine bile acid levels should be monitored intensively (at least every three months during the first year of treatment, every six months during the second year) using suitable analytical techniques. The concentrations of the abnormal bile acid metabolites synthesised in 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency (3β, 7α-dihydroxy- and 3β, 7α, 12α-trihydroxy-5-cholenoic acids) or in Δ^4-3-Oxosteroid-5β-reductase deficiency (3-oxo-7α-hydroxy- and 3-oxo-7α, 12α-dihydroxy-4-cholenoic acids) should be determined. At each investigation, the need for dose adjustment should be considered. The lowest dose of cholic acid that effectively reduces the bile acid metabolites to as close to zero as possible should be chosen.

Patients that have previously been treated with other bile acids or other cholic acid preparations should be closely monitored in the same manner during the initiation of treatment with Orphacol. The dose should be adjusted accordingly, as described above.

Liver parameters should also be monitored, preferentially more frequently than serum and/or urine bile acid levels. Concurrent elevation of serum gamma glutamyltransferase (GGT), alanine aminotransferase (ALT) and/or serum bile acids above normal levels may indicate overdose. Transient elevations of transaminases at the initiation of cholic acid treatment have been observed and do not indicate the need for a dose reduction if GGT is not elevated and if serum bile acid levels are falling or in the normal range.

After the initiation period, serum and/or urine bile acids (using suitable analytical techniques) and liver parameters should be determined annually, at a minimum, and the dose adjusted accordingly. Additional or more frequent investigations should be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy (see section 4.6).

Special populations

Elderly population (≥65 years old)

There is no experience in elderly patients. The dose of cholic acid should be adjusted individually.

Renal impairment

No data are available for patients with renal impairment. The dose of cholic acid should be adjusted individually.

Hepatic impairment

Limited data are available for patients with minor to severe hepatic impairment related to 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency. Patients are expected to present with some degree of hepatic impairment at diagnosis, which improves under cholic acid therapy. The dose of cholic acid should be adjusted individually.

No experience exists in patients with hepatic impairment from causes other than 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency and no dose recommendation can be given. Patients with hepatic impairment should be monitored closely (see section 4.4).

Familial hypertriglyceridemia
Patients with newly diagnosed or a family history of familial hypertriglyceridemia are expected to poorly absorb cholic acid in the intestine. The cholic acid dose for patients with familial hypertriglyceridemia will have to be established and adjusted as described, but an elevated dose, notably higher than the 500 mg daily limit for adult patients, may be required and safe.

Paediatric population
Cholic acid therapy has been used for infants from one month of age, and for children and adolescents. The dose recommendations reflect the use in this population. The daily dose in infants from 1 month to 2 years of age, children and adolescents ranges from 5 to 15 mg/kg and must be adjusted individually for each patient.

Method of administration
Orphacol capsules must be taken with food at approximately the same time each day, in the morning and/or evening. Administration with food may increase cholic acid bioavailability and improve tolerability. Regular and fixed times of administration support the patient's or caregiver's compliance.
Capsules must be swallowed whole with water, without chewing.
For infants and children who cannot swallow capsules, the capsules may be opened and the content added to infant formula or juice. For additional information, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of phenobarbital and primidone with cholic acid (see section 4.5).

4.4 Special warnings and precautions for use

Cases of severe hepatotoxicity, including cases with fatal outcome, have been reported, with the use of cholic acid. Treatment with cholic acid in patients with pre-existing hepatic impairment should be given under close monitoring and, for all patients, should be stopped if abnormal hepatocellular function, as measured by prothrombin time, does not improve within 3 months of the initiation of cholic acid treatment. A concomitant decrease of urine total bile acids should be observed. Treatment should be stopped earlier if there are clear indicators of severe hepatic failure.

Familial hypertriglyceridemia
Patients with newly diagnosed or a family history of familial hypertriglyceridaemia may have poor absorption of cholic acid from the intestine. The dose of cholic acid in such patients should be established and adjusted as described, but an elevated dose, notably higher than the 500 mg daily limit for adult patients, may be required.

Excipients

Orphacol capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Phenobarbital and primidone, which is partially metabolized in phenobarbital, antagonise the effect of cholic acid. Use of phenobarbital or primidone in patients with 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency treated with cholic acid is contraindicated (see section 4.3). Alternative treatments should be used.

Ciclosporin alters the pharmacokinetics of cholic acid by inhibition of the hepatic uptake and hepatobiliary secretion of bile acids, as well as its pharmacodynamics by inhibition of cholesterol 7α-hydroxylase. Co-administration should be avoided. If administration of ciclosporin is considered necessary, serum and urine bile acid levels should be closely monitored and the cholic acid dose adjusted accordingly.

Bile acid sequestrants (cholestyramine, colestipol, colesevelam) and certain antacids (e.g. aluminium hydroxide) bind bile acids and lead to their elimination. Administration of these medicinal products is expected to reduce the effect of cholic acid. The dose of bile acid sequestrants or antacids must be separated from the dose of cholic acid by an interval of 5 hours, regardless of which medicinal product is administered first.

Ursodeoxycholic acid competitively inhibits absorption of other bile acids, including cholic acid, and replaces them in the enterohepatic pool, reducing the effectiveness of negative feedback inhibition on bile acid synthesis provided by oral cholic acid. For patients who are prescribed a combination of ursodeoxycholic acid and cholic acid in single doses, the administration of both medicinal products should be separated: one product should be given in the morning and the other product should be given in the evening, regardless of which medicinal product is given first. For those patients, who are prescribed a combination of ursodeoxycholic acid and cholic acid, in divided doses of cholic acid and/or ursodeoxycholic acid over the day, the administration of these medicinal products should be separated by several hours.

The effect of food on the bioavailability of cholic acid has not been studied. There is a theoretical possibility that administration with food may increase cholic acid bioavailability and improve tolerability.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There is no need for contraceptive measures in women of childbearing potential treated with cholic acid or their partners. Women of childbearing potential should conduct a pregnancy test as soon as a pregnancy is suspected.

Pregnancy
There is a limited amount of data (less than 20 pregnancy outcomes) from the use of cholic acid in pregnant women. The exposed pregnancies showed no adverse reactions to cholic acid and resulted in normal, healthy children. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

It is extremely important that pregnant women continue their therapy during pregnancy. As a precautionary measure, pregnant women and their unborn children should be closely monitored.

Breastfeeding

Cholic acid and its metabolites are excreted in human milk, but at therapeutic doses of Orphacol, no effects on the breastfed newborns/infants are anticipated. Orphacol can be used during breast-feeding.

Fertility
No data on the effects of cholic acid on fertility are available. At therapeutic doses, no effect on fertility is anticipated.

4.7 Effects on ability to drive and use machines

Cholic acid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Due to the rarity of the diseases, the information about the most serious and/or most frequently occurring adverse reactions is limited. Diarrhoea, increased transaminases and pruritus have been associated with overdosage and disappeared after dose reduction. Development of gallstones associated with long-term treatment have been reported in very limited number of patients.

Tabulated list of adverse reactions
The following table lists adverse reactions reported in the literature under treatment with cholic acid. The frequency of these reactions is not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse reaction**
Gastrointestinal disorders	Diarrhoea
Hepatobiliary disorders	Transaminases increased Gallstones
Skin and subcutaneous tissue disorders	Pruritus

Description of selected adverse reactions
The development of pruritus and/or diarrhoea has been observed during treatment with Orphacol. These reactions abated after dose reduction and are suggestive of overdose. Patients presenting with pruritus and/or persistent diarrhoea should be investigated for a potential overdose by a serum and/or urine bile acid assay (see section 4.9).

Gallstones have been reported after long-term therapy.

Paediatric population
The presented safety information is derived principally from paediatric patients. The available literature is not sufficient to detect a difference in the safety of cholic acid within paediatric age groups or between paediatric patients and adults.

Other special populations
Please refer to section 4.2 for use of Orphacol in special populations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Episodes of symptomatic overdose have been reported, including accidental overdose. Clinical features were limited to pruritus and diarrhoea. Laboratory tests showed elevation of serum gamma glutamyltransferase (GGT) transaminases and serum bile acid concentrations. Reduction of the dose led to resolution of the clinical signs and correction of abnormal laboratory parameters.

In the case of an accidental overdose, treatment should be continued at the recommended dose after normalisation of clinical signs and/or biological abnormalities.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, bile acid and derivatives, ATC code: A05AA03

Cholic acid is the predominant primary bile acid in man. In patients with inborn deficiency of 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase and Δ^4-3-Oxosteroid-5β-reductase, the biosynthesis of primary bile acids is reduced or absent. Both inborn diseases are extremely rare, with a prevalence in Europe of about 3 to 5 patients with 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency per 10 million inhabitants, and an estimated ten-fold lower prevalence for Δ^4-3-Oxosteroid-5β-reductase deficiency. In the absence of treatment, unphysiologic cholestatic and hepatotoxic bile acid metabolites are predominant in the liver, serum and urine. The rational basis for treatment consists of restoration of the bile acid-dependent component of bile flow enabling restoration of biliary secretion and biliary elimination of toxic metabolites; inhibition of the production of the toxic bile acid metabolites by negative feedback on cholesterol 7α-hydroxylase, which is the rate-limiting enzyme in bile acid synthesis; and improvement of the patient's nutritional status by correcting intestinal malabsorption of fats and fat-soluble vitamins.

Clinical experience has been reported in the literature from small cohorts of patients and single case reports; absolute patient numbers are small due to the rarity of the conditions. This rarity also made the conduct of controlled clinical studies impossible. Overall, cholic acid treatment results for about 60 patients with 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency are reported in the literature. Detailed long-term data on treatment with cholic acid monotherapy are available for 14 patients observed for up to 12.9 years. Cholic acid treatment results for seven patients with Δ^4-3-Oxosteroid-5β-reductase deficiency for up to 14 years are reported in the literature. Detailed medium- to long-term data are available for 5 of these patients, of whom 1 has been treated with cholic acid monotherapy. Oral cholic acid therapy has been shown to: postpone or obviate the need for liver transplantation; restore normal laboratory parameters; improve histological lesions of the liver, and significantly improve all of the patient's symptoms. Mass spectrometry analysis of urine during cholic acid therapy shows the presence of cholic acid and a marked reduction, or even complete elimination of the toxic bile acid metabolites. This reflects restoration of an effective feedback control of bile acid synthesis and a metabolic equilibrium. In addition, blood cholic acid concentration was normal and fat-soluble vitamins were restored to their normal range.

<u>Paediatric population</u>
The clinical experience reported in the literature is from a patient population with inborn deficiency of 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase or Δ^4-3-Oxosteroid-5β-reductase that includes principally infants from the age of one month, children and adolescents. However, absolute numbers of cases are small.

This medicinal product has been authorised under "Exceptional Circumstances".
This means that due to the rarity of the disease and for ethical reasons it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Cholic acid, a primary bile acid, is partially absorbed in the ileum. The remaining part is transformed by reduction of the 7α-hydroxy group to deoxycholic acid (3α, 12α-dihydroxy) by intestinal bacteria. Deoxycholic acid is a secondary bile acid. More than 90% of the primary and secondary bile acids are reabsorbed in the ileum by a specific active transporter and are recycled to the liver by the portal vein; the remainder is excreted in the faeces. A small fraction of bile acids is excreted in urine.

No pharmacokinetic study data for Orphacol are available.

5.3 Preclinical safety data

The available non-clinical data in the literature reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. The studies have however not been conducted to the same level of detail as for a pharmaceutical agent, as cholic acid is a physiological substance in animals and humans.

The intravenous LD_{50} of cholic acid in mice is 350 mg/kg body weight. Parenteral administration may cause haemolysis and cardiac arrest. Administered orally, bile acids and salts generally have only a minor toxic potential. The oral LD_{50} in mice is 1520 mg/kg. In repeated-dose studies, frequently reported effects of cholic acid have included decreased body weight, diarrhoea and liver damage with elevated transaminases. Increased liver weight and gallstones have been reported in repeated dose studies in which cholic acid was co-administered with cholesterol.

Cholic acid showed non-significant mutagenic activity in a battery of genotoxicity tests performed *in vitro*. Animal studies showed that cholic acid did not induce any teratogenic effect or foetal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate,
Colloidal anhydrous silica,
Magnesium stearate.

Capsule shell Orphacol 50 mg capsule:
Gelatin (bovine origin),
Titanium dioxide (E171),
Carmine blue (E132).

Capsule shell Orphacol 250 mg capsule:
Gelatin (bovine origin),
Titanium dioxide (E171),
Carmine blue (E132),
Yellow Iron Oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister of 10 capsules.
Pack sizes: 30, 60, 120.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use in the paediatric population
See also section 4.2. For infants and children who cannot swallow capsules, the capsules may be opened and the content added to infant formula or infant-adapted apple/orange or apple/apricot juice. Other food such as fruit compote or yoghurt may be suitable for administration, but no data on the compatibility or palatability are available.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Orphacol 50 mg capsule:
EU/1/13/870/001
EU/1/13/870/002
EU/1/13/870/003

Orphacol 250 mg capsule:
EU/1/13/870/004
EU/1/13/870/005
EU/1/13/870/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 September 2013
Date of latest renewal: 24 April 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATIONS TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH, in agreement with the competent authorities in the Member States, shall implement, prior to the launch, an educational programme for physicians aiming to provide educational material on correct diagnosis and therapeutic managements of the treatment of 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 and to inform on expected and potential risks associated with the treatment.

The physician educational programme should contain the following key elements:

- Prescription of a supratherapeutic dose (MedDRA term: drug toxicity)

- Risk of gallstones

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due Date
CTRS commits to monitor the safety and efficacy in patients treated with Orphacol from a patient surveillance database for which the protocol has been endorsed by the CHMP and is documented in the Orphacol RMP. The objectives of this surveillance programme is to monitor accumulating data on efficacy and safety in the treatment of 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 with Orphacol in infants, children, adolescents and adults. Reports on recruitment progress of the patient surveillance database will be analysed and reported to the CHMP at the time of PSURs (for safety) and of the Annual Re-assessments (for efficacy and safety). Progress and results from the database will form the basis of the annual reassessments of the benefit/risk profile of Orphacol.	- PSUR - Annual Re-assessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orphacol 50 mg hard capsules
Orphacol 250 mg hard capsules
Cholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg cholic acid.
Each hard capsule contains 250 mg cholic acid.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoires CTRS
63, rue de l'Est
92100 Boulogne-Billancourt
France
E-mail: ctrs@ctrs.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/870/001 [30 hard capsules]
EU/1/13/870/002 [60 hard capsules]
EU/1/13/870/003 [120 hard capsules]
EU/1/13/870/004 [30 hard capsules]
EU/1/13/870/005 [60 hard capsules]
EU/1/13/870/006 [120 hard capsules]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

AND CONTENTS

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Orphacol 50 mg capsules
Orphacol 250 mg capsules
Cholic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Laboratoires CTRS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Orphacol 50 mg hard capsules
Orphacol 250 mg hard capsules
Cholic acid

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Orphacol is and what it is used for
2. What you need to know before you take Orphacol
3. How to take Orphacol
4. Possible side effects
5. How to store Orphacol
6. Contents of the pack and other information

1. What Orphacol is and what it is used for

Orphacol contains cholic acid, a bile acid which is normally produced by the liver. Certain medical conditions are caused by defects in bile acid production and Orphacol is used to treat infants from one month to 2 years of age, children, adolescents and adults with these medical conditions. The cholic acid contained in Orphacol replaces the bile acids that are missing due to the defect in bile acid production.

2. What you need to know before you take Orphacol

Do not take Orphacol
- if you are allergic to cholic acid or any of the other ingredients of this medicine (listed in section 6).
- if you are taking phenobarbital or primidone, a medicine to treat epilepsy.

Warnings and precautions
During your treatment, your doctor will carry out various blood and urine tests at different time to see how your body is handling this medicine and to help work out the dose that you need. More frequent tests will be needed if you are growing fast, if you are ill (if you have e.g. liver problems), or if you are pregnant.

Other medicines and Orphacol
Tell your doctor or pharmacist if you are taking, have recently taken any or might take other medicines.

Some medicines used to lower cholesterol levels, so-called bile acid sequestrants (cholestyramine, colestipol, colesevelam), and medicines to treat heartburn that contain aluminium may lessen the effect of

Orphacol. If you take these medicines, take Orphacol at least 5 hours before or at least 5 hours after taking these other medicines.
Ciclosporin (a medicine used to suppress the immune system) may also change the effect of Orphacol. Please tell your doctor if you are taking ciclosporin.

Ursodeoxycholic acid may lessen the effect Orphacol if both medicines are taken at the same time. If you are prescribed ursodeoxycholic acid along with Orphacol in single doses, take one product in the morning and the other product in the evening. If you are prescribed divided doses of ursodeoxycholic acid and/or Orphacol, as these products should be administered separately by several hours, please ask for the advice of your doctor or pharmacist about proper sequence of administration.

Pregnancy and breast-feeding
Please consult your doctor if you plan to become pregnant. Take a pregnancy test as soon as you suspect you may be pregnant. It is very important to continue taking Orphacol during pregnancy.

If you become pregnant during treatment with Orphacol, your doctor will decide which treatment and dose is best in your situation. As a precaution, you and your unborn child should be closely monitored during pregnancy.

Orphacol can be used during breast-feeding. Tell your doctor if you plan to breast-feed or are breast-feeding before you take Orphacol.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Orphacol is not expected to have an effect on the ability to drive and use machines.

Orphacol contains lactose
Orphacol contains a certain sugar (lactose monohydrate). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Orphacol.

3. How to take Orphacol

Always take Orphacol exactly as your doctor has told you. Check with your doctor if you are not sure.

The usual starting dose is 5 to 15 mg per kilogram body weight every day in infants, children, adolescents and adults.

Before treatment your doctor will make an assessment from your laboratory tests to determine the correct dose for you. The dose will then be further adjusted by your doctor depending on your body's response.

Orphacol capsules are taken by mouth with a meal at approximately the same time each day, in the morning and/or evening. Taking Orphacol at regular times with a meal will help you remember to take this medicine, and may help your body to better take it up. Capsules must be swallowed whole with water. Do not chew.

If your doctor has prescribed a dose which requires you to take more than one capsule per day, you and your doctor can decide how this will be taken during the day. You may for example take one capsule in the morning and one in the evening. This way, you will have to take fewer capsules at once. However, this might not be possible if you have been prescribed at the same time another medicine containing ursodeoxycholic acid. In this case, you should seek advice from your doctor or pharmacist about proper sequence of administration of ursodeoxycholic acid and Orphacol over the day, as these products should be administered separately by several hours (see section 2).

Use in children
For babies and children who cannot swallow capsules, the capsule can be opened and its contents added to baby formula or apple/orange or apple/apricot juice adapted for small children.

If you take more Orphacol than you should
If you have taken more Orphacol than you should, contact your doctor as soon as possible. He will assess your laboratory test results and advise you when you should resume your treatment with your normal dose.

If you forget to take Orphacol
Take your next dose when you would normally take it. Do not take a double dose to make up for a forgotten dose.

If you stop taking Orphacol
There is a risk of permanently damaging your liver if you stop taking Orphacol. You should never stop taking Orphacol unless your doctor advises you to do so.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Several patients have experienced itching and/or diarrhoea, however, it is not known how likely this is to occur (frequency cannot be estimated from the available data). If itching and/or diarrhoea last for more than three days, tell your doctor.

For several patients an increase of liver enzymes (serum transaminases) have been reported during the treatment with Orphacol (frequency cannot be estimated from the available data). Your doctor will decide what to do if this happens to you.

Gallstones have been reported after long-term therapy with Orphacol.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orphacol

Keep out of the reach and sight of children.

Do not use Orphacol after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Medicines should not be disposed of via wasterwater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Orphacol contains

- The active substance is cholic acid.
  Orphacol 50 mg: Each hard capsule contains 50 mg of cholic acid.
  Orphacol 250 mg: Each hard capsule contains 250 mg of cholic acid.
- The other ingredients are:
  Content of capsules: Lactose monohydrate (see section 2 under 'Orphacol contains lactose' for more information), colloidal anhydrous silica, magnesium stearate
  Capsule shell:
  Orphacol 50 mg: gelatin, titanium dioxide (E171), carmine blue (E132);
  Orphacol 250 mg: gelatin, titanium dioxide (E171), carmine blue (E132), yellow iron oxide (E172).

What Orphacol looks like and contents of the pack

Orphacol is available as hard capsules (capsules) of oblong shape. Capsules of 50 mg cholic acid are blue and white and capsules of 250 mg cholic acid are green and white. They are contained in blisters of 10 capsules each.
Pack sizes are available in 30, 60 and 120 capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Laboratoires CTRS
63, rue de l'Est
92100 Boulogne-Billancourt
France

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Laboratoires CTRS
Tél/Tel: +32 (0)2 40 11 442
ctrs@ctrs.fr

Lietuva
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

България
Laboratoires CTRS
Тел.: + 33 (0)1 707 60 637
ctrs@ctrs.fr

Luxembourg/Luxemburg
Laboratoires CTRS
Tél/Tel: +352 278 62 329
ctrs@ctrs.fr

Česká republika
Laboratoires CTRS
Tel.: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

Danmark
Immedica Pharma AB
Tlf: +46 (0)8 533 39 500
info@immedica.com

Deutschland
Laboratoires CTRS
Tel: +49 (0)3022153008
ctrs@ctrs.fr

Eesti
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

Ελλάδα
Laboratoires CTRS
Τηλ: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

España
Laboratoires CTRS
Tel: + (34) 914 146 613
ctrs@ctrs.fr

France
Laboratoires CTRS
Tél: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

Hrvatska
Medis Adria d.o.o.
Tel: +385 (1) 230 3446
info@medisadria.hr

Ireland
Laboratoires CTRS
Tel: +353 (0)1 695 00 63
ctrs@ctrs.fr

Ísland
Immedica Pharma AB
Sími: + 46 (0)8 533 39 500
info@immedica.com

Magyarország
Medis Hungary Kft
Tel: +36 (2) 380 1028
info@medis.hu

Malta
Laboratoires CTRS
Tel: +356 2776 1358
ctrs@ctrs.fr

Nederland
Laboratoires CTRS
Tel: +31 (0)2 070 38 155
ctrs@ctrs.fr

Norge
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

Österreich
Laboratoires CTRS
Tel: +43 (0)7 208 16 847
ctrs@ctrs.fr

Polska
Laboratoires CTRS
Tel.: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

Portugal
Laboratoires CTRS
Tel: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

România
Laboratoires CTRS
Tel: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

Slovenija
Medis d.o.o.
Tel: +386 (1) 589 6900
info@medis.si

Slovenská republika
Laboratoires CTRS
Tel: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

Italia
Laboratoires CTRS
Tel: +39 (0)800 959 161
ctrs@ctrs.fr

Κύπρος
Laboratoires CTRS
Τηλ: + 33 (0)1 70 76 06 37
ctrs@ctrs.fr

Latvija
Immedica Pharma AB
Tel: +46 (0)8 533 39 500
info@immedica.com

Suomi/Finland
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

Sverige
Immedica Pharma AB
Tel: +46 (0)8 533 39 500
info@immedica.com

United Kingdom (Northern Ireland)
Laboratoires CTRS
Tel: +44 (0)3 301 002 375
ctrs@ctrs.fr

This leaflet was last revised in

This medicine has been authorised under "Exceptional Circumstances".
This means that because of the rarity of this disease and for ethical reasons it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.