資料３－２

調査結果報告書

平成 29 年 6 月 16 日
独立行政法人医薬品医療機器総合機構

Ⅰ．品目の概要

［一　般　名］　別添 1 のとおり
［販　売　名］　別添 1 のとおり
［承認取得者］　別添 1 のとおり
［効能・効果］　別添 1 のとおり
［用法・用量］　別添 1 のとおり
［備　　考］　特になし
［調査担当部］　安全第二部

Ⅱ．今回の調査の経緯

1. 国内における状況

1.1 コデインリン酸塩水和物及びジヒドロコデインリン酸塩

コデインリン酸塩水和物及びジヒドロコデインリン酸塩（以下、コデイン類）は、肝代謝酵素 CYP2D6 により活性代謝産物であるモルヒネ及びジヒドロモルヒネに代謝され、鎮痛、鎮咳等の中枢抑制作用及び止瀉等の末梢作用を示す。

コデイン類は医療用医薬品では単剤と配合剤があり、一般用医薬品としてはかぜ薬及び鎮咳去痰薬に配合されている。医療用医薬品及び一般用医薬品共に、小児の用法及び用量が承認されている品目がある。

コデイン類は副作用として呼吸抑制が知られており、現行、医療用医薬品の添付文書において、「禁忌」、「慎重投与」、「副作用」及び「その他の注意」等の項で呼吸抑制に関する注意喚起がされている。これに加えて、「慎重投与」及び「小児等への投与」の項で、小児では呼吸抑制の感受性が高いことから慎重に投与する必要がある旨の注意喚起がされている。また、一般用医薬品の添付文書に、呼吸抑制に関する注意喚起は記載されていない。

1.2 トラマドール塩酸塩

トラマドール塩酸塩（以下、トラマドール）は、肝代謝酵素 CYP2D6 により活性代謝産物であるモノ-*O*-脱メチル体等に代謝され、鎮痛等の中枢抑制作用を示す。

トラマドールは、医療用医薬品として単剤と配合剤がある。また、小児の用法及び用量が承認されている品目はない。

トラマドールも副作用として呼吸抑制が知られており、現行、添付文書において、「禁忌」、「慎重投与」、「重大な副作用」等の項で呼吸抑制に関する注意喚起がされている。また、「小児等への投与」の項に、小児等における安全性は確立していない旨の注意喚起がされている。

2. 海外における状況

2.1 コデイン類

米国の添付文書において、*Contraindications* の項に扁桃摘除術及び／又はアデノイド切除術を受けた小児における術後疼痛緩和が記載されており、*Boxed Warning* 及び *Warnings and Precautions* の項に、扁桃摘除術又はアデノイド切除術後の疼痛緩和を目的として小児に使用し呼吸抑制の発現及び死亡した例が報告されており、これらの小児は CYP2D6 の Ultra-rapid metabolizers（以下、UM）であった旨の記載がされている（別添 2）。

また、英国の添付文書において、コデインリン酸塩（単剤）では、*Contraindications* の項に、重篤及び生命を脅かす副作用が発現するリスクが増加するため、閉塞性睡眠時無呼吸症候群のため扁桃摘除術又はアデノイド切除術を受けた全ての小児（0～18 歳）、鎮咳治療における 12 歳未満の小児が記載されており、*Therapeutic indications* の項に 12 歳以上の患者における他の鎮痛剤で疼痛緩和ができなかった中等度急性疼痛の治療のみが適応である旨、*Posology and method of administration* の項に鎮痛、鎮咳治療において 12 歳未満の小児は使用すべきではない旨、鎮咳治療において呼吸機能が障害されている 12～18 歳の小児への使用は推奨されない旨、*Special warnings and precautions for use* の項に、小児において閉塞性睡眠時無呼吸のため扁桃摘除術又はアデノイド切除術を受けた後に使用し、稀だが死亡を含む生命を脅かす有害事象が発現するとの文献報告がある旨や、呼吸機能が障害されている可能性のある神経筋障害、重篤な心臓又は呼吸状態、上気道又は肺感染、多発性損傷又は広範な外科的処置等の小児での使用は推奨されない旨が記載されている。ジヒドロコデインリン酸塩では、小児の呼吸抑制に関する記載はない（別添 2）。

2.2 トラマドール

米国の添付文書において、*Pediatric Use* の項に 16 歳以下の患者に対する安全性及び有効性は確立しておらず、小児への投与は推奨されない旨の記載がされている（別添 3）。

また、欧州の添付文書では *Posology and method of administration* の項に 12 歳未満の小児に対する使用は適切ではない旨の記載がされている（別添 3）。

3. 今般の調査に至った経緯

2017 年 4 月、米国食品医薬品局（以下、FDA）は、コデイン類及びトラマドールによる小児の呼吸抑制について、FDA Adverse Event Reporting System（FAERS）においてコデイン

類では死亡例 24 例を含む 64 例の症例（1969 年 1 月から 2015 年 5 月までの期間）及びトラマドールでは死亡例 3 例を含む 9 例の症例（1969 年 1 月から 2016 年 3 月までの期間）が報告されていること等から、コデイン類及びトラマドールを含有する医薬品について、添付文書の *Contraindication* に 12 歳未満の小児への使用を追記し、また、*Warnings* に 12～18 歳の肥満、閉塞性睡眠時無呼吸症候群、重篤な肺疾患等を有する患者への使用は推奨しない旨の記載を追記することを勧告した[1]（別添 4）。また、トラマドールについては、既にコデイン類で呼吸抑制リスクに関して取られていた措置[2]の内容についても反映するため、添付文書の *Contraindications* に 18 歳未満の扁桃摘除術及び／又はアデノイド切除術後の疼痛緩和への使用を追記することも勧告した。なお、コデイン類含有一般用医薬品については、追加の措置を検討中とされている。

当該勧告をふまえ、厚生労働省医薬・生活衛生局安全対策課は平成 29 年 5 月 25 日付けで、独立行政法人医薬品医療機器総合機構（以下、機構）に対して、コデイン類含有医薬品等の安全性に関する調査を依頼した。当該依頼を受けて、機構は、コデイン類含有医薬品及びトラマドールの小児等の呼吸抑制に関する調査を行い、添付文書改訂の必要性について検討を行った。

なお、機構は、調査において専門協議を実施しており、本専門協議の専門委員は、本品目についての専門委員からの申し出等に基づき、「医薬品医療機器総合機構における専門協議等の実施に関する達」（平成 20 年 12 月 25 日付 20 達第 8 号）の規定により、指名した。

III. 機構における調査

1. 国内副作用報告の集積状況

調査対象品目において、2004 年 4 月 1 日から 2017 年 5 月 31 日までに厚生労働省又は機構に報告された 18 歳以下の患者での呼吸抑制関連[3]の重篤副作用報告は、以下のとおりであった。

1.1 コデイン類

医療用医薬品で 2 例、一般用医薬品で 2 例報告があり、死亡例はなかった。いずれも 12 歳未満の小児での症例であり、うち 1 例は一般用医薬品を CYP2D6 の UM である患者が服

[1] FDA HP: FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women（https://www fda.gov/Drugs/DrugSafety/ucm549679 htm）

[2] FDA HP: FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy（https://www fda.gov/Drugs/DrugSafety/ucm339112 htm）

[3] 国際医薬用語集（MedDRA）の高位語（HLT）で「呼吸異常」、「呼吸困難」、「呼吸不全（新生児を除く）」、「意識障害 NEC」、「中毒および毒性」に該当する事象のうち、呼吸抑制が発現している症例を抽出した。

用し、呼吸不全、意識障害等が発現した症例であった。なお、扁桃摘除術又はアデノイド切除術後の症例及び肥満、閉塞性睡眠時無呼吸症候群若しくは重篤な肺疾患を有する患者での症例はなかった（別添 5）。

1.2 トラマドール

該当する副作用報告はなかった（別添 5）。

2. 機構における調査の概要

2.1 コデイン類

コデイン類の国内の副作用報告については、CYP2D6 の UM である 12 歳未満の小児においてコデイン類含有医薬品との因果関係が否定できない呼吸抑制が 1 例報告されており、重篤な転帰を辿っている。また、呼吸抑制関連の重篤な副作用報告症例は全て 12 歳未満の小児であった。さらに、米国においては、呼吸抑制のリスクにより 12 歳未満の小児への投与が制限され、欧州でも同様の勧告がされている[4]。以上の状況を踏まえて、機構は、国内においても米国と同様の対応が必要と判断した。

ただし、コデイン類のモルヒネ等への代謝に関与する CYP2D6 には遺伝子多型があり、遺伝的に CYP2D6 の活性が過剰である UM では、活性代謝産物であるモルヒネ等の生成が速く、モルヒネの血中濃度が上昇し、呼吸抑制等の副作用が発現しやすくなることが知られている[5]。また、CYP2D6 の UM の頻度には人種差があることが知られており、日本人の UM の頻度は欧米人に比べて低い（caucasian：1～10%、日本人：0.5～1%）との報告がある[6]。そのため、国内における小児の呼吸抑制のリスクは欧米と比較して遺伝学的に低いと推定され、国内における死亡症例の報告がないことも踏まえれば、12 歳未満の小児への投与を「禁忌」とする必要はないが、医療用医薬品の添付文書においては、12 歳未満の小児へは投与しない旨の注意喚起を追記すること、一般用医薬品の添付文書においては、呼吸抑制リスクに関する注意喚起を追記したうえで、12 歳未満の小児は医師の診療を優先する旨の注意喚起を追記することが必要と判断した。

[4] EMA HP:
Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation
（http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f）
Codeine not to be used in children below 12 years for cough and cold
（http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f）

[5] Pediatrics 2012; 129(5): e1343-e1347

[6] FDA HP: FDA Briefing Document Joint Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting December 10, 2015
（https://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM475975.pdf）
Clin Pharmacol Ther. 2014; 95: 376-82
Drug Metab Pharmacokinet. 2012; 27: 9-54

なお、米国では、重篤な呼吸抑制のリスクが増加するおそれがあるため、18 歳未満の扁桃摘除術及び／又はアデノイド切除術後の疼痛緩和への使用、及び肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患等を有する 12～18 歳の患者への使用制限も行っている。国内では当該背景を有する患者での副作用は報告されていないが、12 歳未満の小児とリスクは大きく異ならないと考えられるため、肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する 12～18 歳の患者への投与はしない旨、及びコデイン類含有医薬品のうち、効能又は効果から扁桃摘除術及び／又はアデノイド切除術後の疼痛緩和への使用が想定される医薬品において 18 歳未満の当該患者には使用しない旨の注意喚起を添付文書に追記することが適切と判断した。

2.2 トラマドール

国内のトラマドール含有医薬品で小児に対する用法及び用量が承認されている品目はなく、国内における 18 歳以下の患者での呼吸抑制関連の重篤副作用は報告されていない。しかしながら、トラマドールはコデイン類と同様に呼吸抑制リスクがあること、また米国において、小児の重篤な呼吸抑制の症例等があり、コデイン類と同様の措置がとられていることから、トラマドールについてもコデイン類と同様に、12 歳未満の小児へは投与しない旨の注意喚起を追記することが適切と判断した。また、肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する 12～18 歳の患者への投与はしない旨、及びトラマドール含有医薬品のうち、効能又は効果から、扁桃摘除術及び／又はアデノイド切除術後の疼痛緩和への使用が想定される医薬品において 18 歳未満の当該患者には使用しない旨の注意喚起について、コデイン類と同様に添付文書に追記することが必要と判断した。

以上の機構意見について、専門協議を行った。

その結果、12 歳未満の小児、18 歳未満の扁桃摘除術後又はアデノイド切除術後の鎮痛、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者に投与しない旨の注意喚起をする改訂について、専門委員から支持された。

しかしながら、専門委員より、以下の意見が出された。

- 呼吸抑制が生命に直結する合併症であることを考えると本来「禁忌」にするのが妥当と考える。
- CYP2D6 の UM 頻度の人種差や国内症例状況等を理由に 12 歳未満の小児への使用を禁忌とせず注意喚起にとどめることは、説得力に欠ける。
- 12 歳未満の小児の呼吸抑制リスクという観点から言えば、禁忌に記載する方法もあると思われるが、国内には使用している医師も存在しているであろうこと、一般用医薬品にも含有されているものがあること等から、充分な周知のための期間が必要と考える。

専門委員の意見を踏まえ、コデイン類及びトラマドールの小児等への使用について、機構は以下のように考える。

コデイン類による呼吸抑制の重篤性を鑑みると、コデイン類を含有する医療用医薬品については、米国と同様に 12 歳未満の小児及び 18 歳未満の扁桃摘除術後又はアデノイド切除術後の患者については「禁忌」とすることが適切と考える。ただし、投与しない旨を周知する期間が必要であり、また、国内における小児の呼吸抑制リスクは欧米と比較して遺伝学的に低いと推定され、国内における死亡症例の報告がない現状も考慮すると、当面の間は投与しない旨の注意喚起を追記し、一定の期間を経た後に「禁忌」とすることが適切と考える。

また、コデイン類を含有する一般用医薬品についても、医療用医薬品と同様に、一定の期間を経た後に 12 歳未満の小児を「してはいけないこと」に記載することが適切と考える。

トラマドールにおいても、その呼吸抑制リスク及び米国でコデイン類と同様の措置がとられたことをふまえると、コデイン類と同様の対応が適切と考える。

IV. 総合評価

機構は、以下のとおり添付文書の使用上の注意を改訂することが妥当であると判断した。

【改訂案】コデインリン酸塩水和物及びジヒドロコデインリン酸塩（医療用医薬品）

下線部追記、取消線部削除

現行	改訂案
1. 慎重投与（次の患者には慎重に投与すること） ~~新生児、乳児（「小児等への投与」の項参照）~~	1. 慎重投与（次の患者には慎重に投与すること）
2. 重要な基本的注意 記載なし	2. 重要な基本的注意 重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の扁桃摘除術後又はアデノイド切除術後の鎮痛には使用しないこと。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 ~~新生児、乳児では低用量から投与を開始するなど患者の状態を観察しながら、慎重に投与すること。~~［呼吸抑制の感受性が高い。］	7. 小児等への投与 12 歳未満の小児には投与しないこと。［呼吸抑制の感受性が高い。海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］

【改訂案】コデインリン酸塩水和物・オウヒエキス（医療用医薬品）
ジヒドロコデインリン酸塩・キキョウ流エキス・カンゾウエキス・シャゼンソウエキス・シャクヤクエキス（医療用医薬品）
下線部追記、取消線部削除

現行	改訂案
1. 慎重投与（次の患者には慎重に投与すること） ~~新生児、乳児（「小児等への投与」の項参照）~~	1. 慎重投与（次の患者には慎重に投与すること）
2. 重要な基本的注意 記載なし	2. 重要な基本的注意 重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 ~~新生児、乳児には低用量から投与を開始するなど患者の状態を観察しながら、慎重に投与すること。~~［呼吸抑制の感受性が高い。］	7. 小児等への投与 12 歳未満の小児には投与しないこと。［呼吸抑制の感受性が高い。海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］

【改訂案】ジヒドロコデインリン酸塩・*dl*-メチルエフェドリン塩酸塩・クロルフェニラミンマレイン酸塩（医療用医薬品）

下線部追記、取消線部削除

現行	改訂案
1. 慎重投与（次の患者には慎重に投与すること） ~~乳児、~~高齢者、衰弱者［~~新生児、乳児は代謝が不十分であり、~~高齢者、衰弱者は代謝・排泄機能が低下しているため、副作用が発現するおそれがある（「高齢者への投与」~~、「小児等への投与」~~の項参照）］。	1. 慎重投与（次の患者には慎重に投与すること） 高齢者、衰弱者［高齢者、衰弱者は代謝・排泄機能が低下しているため、副作用が発現するおそれがある（「高齢者への投与」の項参照）］。
2. 重要な基本的注意 記載なし	2. 重要な基本的注意 重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 ~~新生児、乳児では低用量から投与を開始するなど患者の状態を観察しながら、慎重に投与すること。~~［呼吸抑制の感受性が高い。］	7. 小児等への投与 12 歳未満の小児には投与しないこと。［呼吸抑制の感受性が高い。海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］

【改訂案】ジヒドロコデインリン酸塩・ジプロフィリン・*dl*-メチルエフェドリン塩酸塩・ジフェンヒドラミンサリチル酸塩・アセトアミノフェン・ブロモバレリル尿素（医療用医薬品）

下線部追記、取消線部削除

現行	改訂案
1. 慎重投与（次の患者には慎重に投与すること） 小児~~等~~［「小児等への投与」の項参照］	1. 慎重投与（次の患者には慎重に投与すること） 12 歳以上の小児［「小児等への投与」の項参照］
2. 重要な基本的注意 用法・用量どおり正しく使用しても効果が認められない場合は、本剤が適当でないと考えられるので、投与を中止すること。 なお、小児に投与する場合には、使用法を正しく指導し、経過の観察を十分行うこと。	2. 重要な基本的注意 用法・用量どおり正しく使用しても効果が認められない場合は、本剤が適当でないと考えられるので、投与を中止すること。 なお、12 歳以上の小児に投与する場合には、使用法を正しく指導し、経過の観察を十分行うこと。
記載なし	重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 小児~~等~~には副作用の発現に特に注意し、必要最小限の使用にとどめるなど慎重に投与すること。［呼吸抑制の感受性が高い。小児等に	7. 小児等への投与 12 歳未満の小児には投与しないこと。［呼吸抑制の感受性が高い。海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリス

対する安全性は確立していない。］	クが高いとの報告がある。］ 12 歳以上の小児には副作用の発現に特に注意し、必要最小限の使用にとどめるなど慎重に投与すること。［呼吸抑制の感受性が高い。小児等に対する安全性は確立していない。］

【改訂案】ジヒドロコデインリン酸塩・エフェドリン塩酸塩・塩化アンモニウム（医療用医薬品）

下線部追記、取消線部削除

現行	改訂案
1. 慎重投与（次の患者には慎重に投与すること） ~~新生児、乳児（「小児等への投与」の項参照）~~	1. 慎重投与（次の患者には慎重に投与すること）
2. 重要な基本的注意 用法・用量どおり正しく使用しても効果が認められない場合は、本剤が適当でないと考えられるので、投与を中止すること。 なお、小児に投与する場合には、使用法を正しく指導し、経過の観察を十分に行うこと。	2. 重要な基本的注意 用法・用量どおり正しく使用しても効果が認められない場合は、本剤が適当でないと考えられるので、投与を中止すること。 なお、12 歳以上の小児に投与する場合には、使用法を正しく指導し、経過の観察を十分に行うこと。
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7. 小児等への投与 ~~新生児、乳児では低用量から投与を開始するなど患者の状態を観察しながら、慎重に投与すること。~~［呼吸抑制の感受性が高い。］	7. 小児等への投与 12 歳未満の小児には投与しないこと。［呼吸抑制の感受性が高い。海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］

【改訂案】コデインリン酸塩水和物含有製剤及びジヒドロコデインリン酸塩含有製剤（一般用医薬品・12 歳未満の用法を有する製剤）

下線部追記

<table>
<tr><th>現行</th><th>改訂案</th></tr>
<tr><td>「相談すること」
1．次の人は服用前に医師、薬剤師又は登録販売者に相談すること。
次の診断を受けた人。
記載なし

2．服用後、次の症状があらわれた場合は副作用の可能性があるので、直ちに服用を中止し、この文書を持って医師、薬剤師又は登録販売者に相談すること。
略
まれに下記の重篤な症状が起こることがある。その場合は直ちに医師の診療を受けること。
<table><tr><th>症状の名称</th><th>症　　状</th></tr><tr><td>略</td><td>略</td></tr></table>
「用法及び用量に関連する注意」
記載なし</td><td>「相談すること」
1．次の人は服用前に医師、薬剤師又は登録販売者に相談すること。
次の診断を受けた人。
<u>呼吸機能障害、閉塞性睡眠時無呼吸症候群、肥満症</u>

2．服用後、次の症状があらわれた場合は副作用の可能性があるので、直ちに服用を中止し、この文書を持って医師、薬剤師又は登録販売者に相談すること。
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「用法及び用量に関連する注意」
<u>12 歳未満の小児には、医師の診療を受けさせることを優先すること。</u></td></tr>
</table>

【改訂案】コデインリン酸塩水和物含有製剤及びジヒドロコデインリン酸塩含有製剤（一般用医薬品・12 歳未満の用法を有しない製剤）

下線部追記

<table>
<tr><th>現行</th><th>改訂案</th></tr>
<tr><td>「相談すること」
1. 次の人は服用前に医師、薬剤師又は登録販売者に相談すること。
次の診断を受けた人。
記載なし

2. 服用後、次の症状があらわれた場合は副作用の可能性があるので、直ちに服用を中止し、この文書を持って医師、薬剤師又は登録販売者に相談すること。
略
まれに下記の重篤な症状が起こることがある。その場合は直ちに医師の診療を受けること。
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1. 次の人は服用前に医師、薬剤師又は登録販売者に相談すること。
次の診断を受けた人。
<u>呼吸機能障害、閉塞性睡眠時無呼吸症候群、肥満症</u>

2. 服用後、次の症状があらわれた場合は副作用の可能性があるので、直ちに服用を中止し、この文書を持って医師、薬剤師又は登録販売者に相談すること。
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まれに下記の重篤な症状が起こることがある。その場合は直ちに医師の診療を受けること。
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</table>

【改訂案】トラマドール塩酸塩（注射剤）

下線部追記、取消線部削除

現行	改訂案
2. 重要な基本的注意 記載なし	2. 重要な基本的注意 重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の扁桃摘除術後又はアデノイド切除術後の鎮痛には使用しないこと。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 ~~小児等~~への投与に関する安全性は確立されていないので、投与しないことが望ましい（使用経験がない）。	7. 小児等への投与 12 歳未満の小児には投与しないこと。［海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］ 12 歳以上の小児への投与に関する安全性は確立されていないので、投与しないことが望ましい（使用経験がない）。

【改訂案】トラマドール塩酸塩（経口剤）

下線部追記、取消線部削除

現行	改訂案
2. 重要な基本的注意 記載なし	2. 重要な基本的注意 重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 ~~小児等~~への投与に関する安全性は確立されていない（使用経験がない）。	7. 小児等への投与 12 歳未満の小児には投与しないこと。［海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］ 12 歳以上の小児への投与に関する安全性は確立されていない（使用経験がない）。

【改訂案】トラマドール塩酸塩・アセトアミノフェン

下線部追記、取消線部削除

現行	改訂案
2. 重要な基本的注意 記載なし	2. 重要な基本的注意 重篤な呼吸抑制があらわれるおそれがあるので、12 歳未満の小児には投与しないこと（「小児等への投与」の項参照）。 重篤な呼吸抑制のリスクが増加するおそれがあるので、18 歳未満の肥満、閉塞性睡眠時無呼吸症候群又は重篤な肺疾患を有する患者には投与しないこと。
7. 小児等への投与 ~~低出生体重児、新生児、乳児、幼児又は~~小児における安全性は確立していない。	7. 小児等への投与 12 歳未満の小児には投与しないこと。［海外において、12 歳未満の小児で死亡を含む重篤な呼吸抑制のリスクが高いとの報告がある。］ 12 歳以上の小児における安全性は確立していない。

別添 1

コデインリン酸塩水和物及びジヒドロコデインリン酸塩（医療用医薬品）

一般名	販売名	承認取得者	効能・効果	用法･用量
コデインリン酸塩水和物	コデインリン酸塩散 1%「第一三共」、同散 10%「第一三共」、同「第一三共」原末、同錠 20mg「第一三共」、同錠 5mg「シオエ」　他	第一三共株式会社、第一三共プロファーマ、シオエ製薬株式会社　他	各種呼吸器疾患における鎮咳・鎮静、疼痛時における鎮痛、激しい下痢症状の改善	通常、成人には、コデインリン酸塩水和物として 1 回 20mg、1 日 60mg を経口投与する。なお、年齢、症状により適宜増減する。
ジヒドロコデインリン酸塩	ジヒドロコデインリン酸塩散 1%「第一三共」、同散 10%「第一三共」､同「第一三共」原末　他	第一三共株式会社、第一三共プロファーマ　他	各種呼吸器疾患における鎮咳・鎮静、疼痛時における鎮痛、激しい下痢症状の改善	通常、成人には、ジヒドロコデインリン酸塩として、1 回 10mg、1 日 30mg を経口投与する。なお、年齢、症状により適宜増減する。
コデインリン酸塩水和物・オウヒエキス	サリパラ・コデイン液	丸石製薬株式会社	下記疾患に伴う咳嗽及び喀痰喀出困難 急性気管支炎、感冒・上気道炎、肺結核	通常、成人 1 回 1.5～2mL を 1 日 3 回、白湯又は砂糖湯で 2～3 倍に薄めて、経口投与する。なお、年齢、症状により適宜増減する。
ジヒドロコデインリン酸塩・*dl* - メチルエフェドリン塩酸塩・ クロルフェニラミンマレイン酸塩	ライトゲン配合シロップ他	帝人ファーマ株式会社　他	下記疾患に伴う咳嗽 急性気管支炎、慢性気管支炎、感冒・上気道炎、肺炎、肺結核	通常成人 1 日 10mL を 3 回に分割経口投与する。なお、症状により適宜増減する。 乳幼小児には以下のように投与する。 12 歳以上 15 歳未満：成人量の 2/3 8 歳以上 12 歳未満：成人量の 1/2 5 歳以上 8 歳未満：成人量の 1/3 2 歳以上 5 歳未満：成人量の 1/5 2 歳未満：成人量の 1/10

	フスコデ配合錠　他	マイラン EPD 合同会社　他		通常成人 1 日 9 錠を 3 回に分割経口投与する。 なお、症状により適宜増減する。 乳幼小児には以下のように投与する。 12 歳以上 15 歳未満：成人量の 2/3 8 歳以上 12 歳未満：成人量の 1/2 5 歳以上 8 歳未満：成人量の 1/3 2 歳以上 5 歳未満：成人量の 1/5 2 歳未満：成人量の 1/10
	ニチコデ配合散　他	日医工株式会社他		通常成人 1 日 3g を 3 回に分割経口投与する。 なお、症状により適宜増減する。 乳幼小児には以下のように投与する。 12 歳以上 15 歳未満：成人量の 2/3 8 歳以上 12 歳未満：成人量の 1/2 5 歳以上 8 歳未満：成人量の 1/3 2 歳以上 5 歳未満：成人量の 1/5 2 歳未満：成人量の 1/10
ジヒドロコデインリン酸塩・ジプロフィリン・*dl*-メチルエフェドリン塩酸塩・ジフェンヒドラミンサリチル酸塩・アセトアミノフェン・ブロモバレリル尿素	カフコデ N 配合錠	ファイザー株式会社	かぜ症候群における鎮咳、鎮痛、解熱 気管支炎における鎮咳	通常、成人には 1 回 2 錠、1 日 3 回経口投与する。なお、小児には年齢により、適宜減量する。

ジヒドロコデインリン酸塩・キキョウ流エキス・カンゾウエキス・シャゼンソウエキス・シャクヤクエキス	オピセゾールコデイン液	日医工株式会社	次の疾患に伴う咳嗽及び喀痰喀出困難 上気道炎、急性気管支炎	通常成人 1 日 4～6mL を 3 回に分けて経口投与する。なお、年齢、症状により適宜増減する。
ジヒドロコデインリン酸塩・エフェドリン塩酸塩・塩化アンモニウム	セキコデ配合シロップ	日医工株式会社	下記疾患に伴う咳嗽および喀痰喀出困難 急性気管支炎、慢性気管支炎、感冒・上気道炎	通常成人 1 回 3～5mL を 1 日 3 回食後または食間にそのまま，または白湯でうすめて経口投与する。 11～14 歳：成人量の 2/3 8～10 歳：成人量の 1/2 5～7 歳：成人量の 1/3 3～4 歳：成人量の 1/4 1～2 歳：成人量の 1/5 3 ヵ月以上 1 歳未満：成人量の 1/10

コデインリン酸塩水和物及びジヒドロコデインリン酸塩（一般用医薬品）

一般名	販売名	承認取得者	効能・効果	用法･用量
ジヒドロコデインリン酸塩含有製剤	パブロンゴールド A、新ルルーA 錠 s、ベンザブロック L　他	大正製薬株式会社、第一三共ヘルスケア株式会社、武田コンシューマーヘルスケア株式会社　他	かぜの諸症状（鼻水、鼻づまり、くしゃみ、のどの痛み、せき、たん、悪寒（発熱によるさむけ）、発熱、頭痛、関節の痛み、筋肉の痛み）の緩和 [1)]	用法は、1 日 3 回食後なるべく 30 分以内に服用するものとする。ただし、シロップ剤については、毎食後及び必要な場合には就寝前に服用するものとし、また、場合によっては、1 日 6 回まで服用することとしても差し支えないが 1 日 6 回服用する場合には原則として約 4 時間の間隔をおいて服用するものとしなければならない。[1)]
ジヒドロコデインリン酸塩含有製剤	新ブロン液エース、新トニン咳止め液、クールワンせき止め GX　他	エスエス製薬株式会社、佐藤製薬株式会社、テイカ製薬株式会社　他	せき、喘鳴（ぜーぜー、ひゅーひゅー）をともなうせき、たん [2)]	用法は 1 日 3～4 回服用するものとし、服用時期又は服用間隔を明記すること。ただし、トローチ剤、ドロップ剤、経口液剤及びシロップ剤については、1 日 6 回まで服用することとしても差し支えないが、1 日 5～6 回服用する場合には原則としてトローチ剤及びドロップ剤にあっては 2 時間以上、経口液剤及びシロップ剤にあっては約 4 時間の間隔をおいて服用するものとしなければならない。[2)]
コデインリン酸塩水和物含有製剤	アネトンせき止め液　他	ジョンソン・エンド・ジョンソン株式会社		

1)「かぜ薬の製造販売承認基準について」（平成 27 年 3 月 25 日付薬食発 0325 第 28 号）より抜粋

2)「「鎮咳去痰薬の製造販売承認基準について」の一部改正について」（平成 28 年 3 月 28 日付薬生発 0328 第 10 号）より抜粋

トラマドール（医療用医薬品）

一般名	販売名	承認取得者	効能・効果	用法･用量
トラマドール塩酸塩	トラマール注 100	日本新薬株式会社	下記疾患ならびに状態における鎮痛 各種癌、術後	通常成人にはトラマドール塩酸塩として 1 回 100～150mg を筋肉内に注射し、その後必要に応じて 4～5 時間毎に反復注射する。なお、症状により適宜増減する。
	トラマール OD 錠 25mg、同 OD 錠 50mg	日本新薬株式会社	非オピオイド鎮痛剤で治療困難な下記疾患における鎮痛 疼痛を伴う各種癌 慢性疼痛	通常、成人にはトラマドール塩酸塩として 1 日 100～300mg を 4 回に分割経口投与する。なお、症状に応じて適宜増減する。ただし 1 回 100mg、1 日 400mg を超えないこととする。
	ワントラム錠 100mg	日本新薬株式会社	非オピオイド鎮痛剤で治療困難な下記における鎮痛 疼痛を伴う各種癌 慢性疼痛	通常、成人にはトラマドール塩酸塩として 100～300mg を 1 日 1 回経口投与する。なお、症状に応じて適宜増減する。ただし、1 日 400mg を超えないこととする。
トラマドール塩酸塩・アセトアミノフェン	トラムセット配合錠	ヤンセンファーマ株式会社	非オピオイド鎮痛剤で治療困難な下記疾患における鎮痛 非がん性慢性疼痛 抜歯後の疼痛	非がん性慢性疼痛 通常、成人には、1 回 1 錠、1 日 4 回経口投与する。投与間隔は 4 時間以上空けること。 なお、症状に応じて適宜増減するが、1 回 2 錠、1 日 8 錠を超えて投与しないこと。また、空腹時の投与は避けることが望ましい。 抜歯後の疼痛 通常、成人には、1 回 2 錠を経口投与する。 なお、追加投与する場合には、投与間隔を 4 時間以上空け、1 回 2 錠、1 日 8 錠を超えて投与しないこと。また、空腹時の投与は避けることが望ましい。

海外添付文書における関連記載の記載状況

コデインリン酸塩水和物（単剤）

米国（USPI） CODEINE SULFATE TABLETS（West-Ward Pharmaceuticals Corp.） 2016 年 12 月改訂	**英国（UK SPC）** Codeine Phosphate Tablets 15mg（Actavis UK Ltd） 2016 年 10 月改訂
BOXED WARNING **Death Related to Ultra-Rapid Metabolism of Codeine to Morphine** Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.[see Warnings and Precautions(5.3)]	—
1 INDICATIONS AND USAGE Codeine Sulfate Tablets are indicated for the management of mild to moderate pain, where treatment with an opioid is appropriate and for which alternative treatments are inadequate. *Limitations of Use* Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions (5.1)], reserve Codeine Sulfate Tablets for use in patients for whom alternative treatment options [e.g., nonopioid analgesics or opioid combination products]: ・ Have not been tolerated, or are not expected to be tolerated, ・ Have not provided adequate analgesia, or are not expected to provide adequate analgesia	**4. Clinical particulars** **4.1 Therapeutic indications** 1） Indicated as an analgesic for the relief of mild to moderate pain. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone). 2） For the symptomatic relief of unproductive cough and diarrhoea.
2 DOSAGE AND ADMINISTRATION **2.1 Important Dosage and Administration Instructions** Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)]. Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)].	**4.2 Posology and method of administration** Long term use – the risk benefit should be assessed regularly by the prescriber. Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose should not exceed 240mg. The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician *Posology*

米国（USPI）	英国（UK SPC）
Monitor patients closely for respiratory depression, especially within the first 24 - 72 hours of initiating therapy and following dosage increases with Codeine Sulfate Tablets and adjust the dosage accordingly [see Warnings and Precautions (5.2)]. **2.2 Initial Dosage** *Initiating Treatment with Codeine Sulfate Tablets* Initiate treatment with Codeine Sulfate Tablets in a dosing range of 15 to 60 mg every 4 hours as needed for pain. Adult doses of Codeine Sulfate Tablets higher than 60 mg provide no further efficacy but are associated with greater adverse reactions. The maximum 24 hour dose is 360 mg. *Conversion from Other Opioids to Codeine Sulfate Tablets* There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of Codeine Sulfate Tablets. It is safer to underestimate a patient's 24-hour Codeine Sulfate Tablets dosage than to overestimate the 24-hour Codeine Sulfate Tablets dosage and manage an adverse reaction due to overdose. **2.3 Titration and Maintenance of Therapy** Individually titrate Codeine Sulfate Tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving codeine sulfate to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.1)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Codeine Sulfate Tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions. **2.4 Discontinuation of Codeine Sulfate Tablets** When a patient who has been taking Codeine Sulfate Tablets regularly and may be	*Analgesia* Adults: 30-60mg every four hours to a maximum dosage of 240mg daily. The analgesic effect is not materially enhanced by increasing the dose to a greater level than that recommended above. Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function. Paediatric population: Children aged 12 years to 18 years: The recommended codeine dose for children 12 years and older should be 30 to 60 mg every 6 hours when necessary up to a maximum dose of 240mg daily. The dose is based on the body weight (0.5-1mg/kg). Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4). *Diarrhoea* Adults and children over 12 years: 15-60mg three to four times daily. Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function. Children under 12 years: Not recommended. *Cough* Adults and children over 12 years: 15-30mg three to four times daily. Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function. Paediatric population: *Children aged 12 years to 18 years:* Codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough (see section 4.4). *Children aged less than 12 years:* Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough (see sections 4.3). Method of Administration

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physically dependent no longer requires therapy with Codeine Sulfate Tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Codeine Sulfate Tablets in a physically-dependent patient[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)].	For oral use.
4 CONTRAINDICATIONS Codeine Sulfate Tablets are contraindicated in patients with: （略） ・ Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy [see Warnings and Precautions (5.4)]	**4.3 Contraindications** （略） ・ In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4) ・ In children below the age of 12 years for the symptomatic treatment of cough due to an increased risk of developing serious and life-threatening adverse reactions. （略） ・ In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers
5 WARNINGS AND PRECAUTIONS **5.4 Death Related to Ultra-Rapid Metabolism of Codeine to Morphine** Codeine Sulfate Tablets are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)]. Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine [see Use in Specific Populations (8.4)]. Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in	**4.4 Special warnings and precautions for use** （略） CYP2D6 metabolism （略） Post-operative use in children There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine. Children with compromised respiratory function Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures.

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North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)]. Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine.	These factors may worsen symptoms of morphine toxicity.
8 USE IN SPECIFIC POPULATIONS **8.4 Pediatric Use** The safety and effectiveness and the pharmacokinetics of Codeine Sulfate Tablets in pediatric patients below the age of 18 have not been established. Respiratory depression and death have occurred in children with obstructive sleep apnea who received Codeine Sulfate Tablets in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)].	—

米国（USPI）	英国（UK SPC）
17 PATIENT COUNSELING INFORMATION （略） *Ultra-Rapid Codeine Metabolizers* Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are ultra-rapid codeine metabolizers or not. These higher-than-normal levels of morphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing [see Warnings and Precautions (5.4)]. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Codeine is contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine for other reasons to monitor for signs of respiratory depression.	—

コデインリン酸塩水和物（配合剤）

米国（USPI） Promethazine and Codeine（Par Pharmaceutical） 2017 年 1 月改訂	英国（UK SPC） Boots Paracetamol and Codeine Extra Capsules（THE BOOTS COMPANY PLC） 2017 年 3 月改訂
BOXED WARNING **Respiratory Depression in Children** The combination of promethazine　hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age. Concomitant administration of promethazine products with other respiratory depressants has an association with respiratory depression, and sometimes death, in pediatric patients. Postmarketing cases of respiratory depression, including fatalities, have been reported with use of promethazine hydrochloride in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride have resulted in respiratory depression in these patients. **Death Related to Ultra-Rapid Metabolism of Codeine to Morphine** Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.	—
INDICATIONS AND USAGE Promethazine with Codeine Oral Solution is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.	**4. Clinical particulars** **4.1 Therapeutic indications** This medicine is indicated in patients older than 12 years of age. For the fast relief of pain. For the short term treatment of acute moderate pain which is not considered to be relieved by other analgesics (e.g. paracetamol, ibuprofen or aspirin alone such as: headache, migraine, period pain, dental pain, neuralgia and rheumatic pain (including muscular pain and backache).
DOSAGE AND ADMINISTRATION It is important that Promethazine with Codeine Oral Solution is measured with an accurate measuring device (see PRECAUTIONS-Information for Patients). A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is to be measured. It is strongly recommended that an accurate measuring device be used. A pharmacist can provide an appropriate device and can provide instructions for	**4.2 Posology and method of administration** Adults Two capsules to be taken up to four times a day, doses being repeated not more than every four hours, up to amaximum of eight capsules in 24 hours. Children aged 16 to 18 years One or two capsules every 6 hours when necessary up to a maximum of eight capsules in 24

米国（USPI）	英国（UK SPC）
measuring the correct dose. The combination of promethazine hydrochloride and codeine phos phate is contraindicated in pediatric patients les s than 6 years of age, becaus e the combination may caus e fatal res piratory depres s ion in this age population. The average effective dose is given in the following table: Adults (12 years of age and over) 5 mL (1 teaspoonful) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours. Children 6 years to under 12 years 2.5 mL to 5 mL (½ to 1 teaspoonful) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours.	hours Children aged 12 to 15 years One capsule every 6 hours when necessary up to a maximum of 4 capsules in 24 hours. Children under 12 years Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4). Elderly There is no need for dosage reduction in the elderly. Do not take for more than 3 days continuously without medical review.
CONTRAINDICATIONS The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population. Codeine sulfate is contraindicated for post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy. (See WARNINGS - Death Related to Ultra- Rapid Metabolism of Codeine to Morphine).	**4.3 Contraindications** （略） In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life threatening adverse reactions (see section 4.4). In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
WARNINGS (see Boxed Warnings) **Respiratory Depression in Children** The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age. Concomitant administration of promethazine products with other respiratory depressants has an association with respiratory depression, and sometimes death, in pediatric patients. Postmarketing cases of respiratory depression, including fatalities, have been reported with use of promethazine hydrochloride in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride have resulted in respiratory depression in these patients. Respiratory depression leading to arrest, coma, and death has occurred with the use of codeine antitussives in young children, particularly in the under-one-year infants whose ability to deactivate the drug is not fully developed.	**4.4 Special warnings and precautions for use** Do not give to children under 12. （略） CYP2D6 metabolism （略） Post operative use in children There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events including death(see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine. Children with compromised respiratory function

米国（USPI）	英国（UK SPC）
Codeine **・Death Related to Ultra-Rapid Metabolism of Codeine to Morphine** Respiratory depression and death have occurred in children who received codeine in the post- operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine. (See PRECAUTIONS -Nursing Mothers). Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). (See OVERDOSAGE). Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy. (See CONTRAINDICATIONS). When prescribing codeine-containing drugs, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose. (See OVERDOSAGE). （略） **Use in Pediatric Patients** The combination of promethazine hydrochloride and codeine phosphate is contraindicated	Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

米国（USPI）	英国（UK SPC）
in pediatric patients less than 6 years of age. Concomitant administration of promethazine products with other respiratory depressants has an association with respiratory depression, and sometimes death, in pediatric patients. The association does not directly relate to individualized weight-based dosing, which might otherwise permit safe administration. Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in these patients. (See WARNINGS- Death Related to Ultra-Rapid Metabolism of Codeine to Morphine and CONTRAINDICATIONS). （略）	
PRECAUTIONS **Information for Patients** （略） Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid codeine metabolizer or not. These higher-than-normal levels of morphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. As a result, codeine is contraindicated in children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine for other reasons to monitor for signs of respiratory depression. (See WARNINGS - Death Related to Ultra-Rapid Metabolism of Codeine to Morphine). （略） **Pediatric Use** The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population (see WARNINGS – Boxed Warning and Use in	—

米国（**USPI**）	英国（**UK SPC**）
Pediatric Patients). Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy. (See WARNINGS - Death Related to Ultra-Rapid Metabolism of Codeine to Morphine and CONTRAINDICATIONS).	

ジヒドロコデインリン酸塩（単剤）

米国（USPI）	英国（UK SPC）
販売なし	Dihydrocodein Tablets BP 30mg（Actavis UK Ltd） 2016 年 8 月改訂
―	**4. Clinial particulars** **4.1 Therapeutic indications** 1) As an analgesic for the relief of moderate to severe pain. Dihydrocodeine Tablets 30mg are indicated in all painful conditions where an alert patient is desired, *eg* sciatica, osteo-arthritis, chronic rheumatoid arthritis, arthritis of the spine, peripheral vascular disease, post-herpetic neuralgia, Paget's disease, malignant disease, post-operative pain. Because dihydrocodeine, in the recommended doses, causes little or no respiratory depression, its use in the treatment of post-operative pain may reduce the risk of chest complications.
―	**4.2 Posology and method of administration** <u>Posology</u> The analgesic effect is not materially enhanced by increasing the dose above that recommended below; in severe cases the interval between doses should be reduced to obtain the requisite analgesic cover. *Adults:* 1 tablet every four to six hours or at the discretion of the practitioner. *Paediatric population:* A more suitable dosage form is recommended for children under 12 years (e.g. elixir). *Elderly:* Dosage should be reduced in the elderly. <u>Method of administration</u> For oral use. It is recommended that this product should be taken during or after food.

ジヒドロコデインリン酸塩（配合剤）

米国（USPI） SYNALGOS®-DC（Sun Pharmaceutical Industries,Inc） 2016 年 12 月改訂	英国（UK SPC） Co-dydramol 10/500mg Tablets（Wockhardt UK Ltd） 2017 年 5 月改訂
BOXED WARNING **<u>Death Related to Ultra-Rapid Metabolism of Dihydrocodeine to Dihydromorphine</u>** Respiratory depression and death have occurred in children who received dihydrocodeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of dihydrocodeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high dihydromorphine concentrations) [see Warnings and Precautions (5.4)].	—
1 INDICATIONS AND USAGE SYNALGOS-DC is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. <u>Limitations of Use</u> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions (5.1)],reserve SYNALGOS-DC for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]: ・ Have not been tolerated, or are not expected to be tolerated, ・ Have not provided adequate analgesia, or are not expected to provide adequate analgesia	**4. Clinical particulars** **4.1 Therapeutic indications** Co-dydramol tablets are indicated for the relief of mild to moderate pain in musculoskeletal conditions (e.g. sciatica, osteoarthritis, chronic rheumatoid arthritis, sprains, strains etc.)
2 DOSAGE AND ADMINISTRATION **2.1 Important Dosage and Administration Instructions** Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings andPrecautions (5)]. Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with SYNALGOS-DC and adjust the	**4.2 Posology and method of administration** ***Adults and children 16 years and over:*** *Analgesia:* One to two tablets every four to six hours. Do not take more than 8 tablets in 24 hours. ***Children 12 – 15 years:*** One tablet every 4-6 hours when necessary to a maximum of 4 doses in any 24 hours. ***Children under 12 years of age:*** Do not give to children under 12 years. *Elderly:*

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dosage accordingly [see Warnings and Precautions (5.2)]. Administer SYNALGOS-DC with food or a full glass of water to minimize GI distress. SYNALGOS-DC is not recommended for patients 12 years and under [see Use in Specific Populations (8.4)]. **2.2 Initial Dosage** Initiating Treatment with SYNALGOS-DC Initiate treatment in adults with two capsules of SYNALGOS-DC orally every 4 hours as needed for pain. Conversion from Other Opioids to SYNALGOS-DC There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of SYNALGOS-DC. It is safer to underestimate a patient's 24-hour SYNALGOS-DC dosage than to overestimate the 24-hour SYNALGOS-DC dosage and manage an adverse reaction due to overdose. **2.3 Titration and Maintenance of Therapy** Individually titrate SYNALGOS-DC to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving SYNALGOS-DC to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.1)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the SYNALGOS-DC dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions. **2.4 Discontinuation of SYNALGOS-DC** When a patient who has been taking SYNALGOS-DC regularly and may be physically	The initial dose should be reduced in the elderly and subsequently adjusted according to response. Hepatic impairment: A reduction in dosage should be considered (see also 4.8 Undesirable Effects) Renal impairment: The dosage should be reduced in moderate to severe renal impairment (see also 4.8 Undesirable Effects) For concomitant illnesses/conditions where dose reduction may be appropriate, see 4.4 Special Warnings and Precautions for Use. Method of administration For oral use.

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dependent no longer requires therapy with SYNALGOS-DC, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue SYNALGOS-DC in a physically dependent patient [see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)].	
4 CONTRAINDICATIONS SYNALGOS-DC is contraindicated in patients with: （略） •Postoperative pain management in children who have under-gone tonsillectomy and/or adenoidectomy [see Warnings and Precautions (5.4)]	**4.3 Contraindications** （略） Not to be given tochildren under twelve years.
5 WARNINGS AND PRECAUTIONS **5.4 Risk of Death Related to Ultra-Rapid Metabolism of Dihydrocodeine to Dihydromorphine** Because of comparable metabolic pathways for codeine and dihydrocodeine and similar potencies for codeine and dihydrocodeine and morphine and dihydromorhine, the risks associated with ultra-rapid metabolism of codeine are present for dihyrodcodeine. Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine [see Use in Specific Populations (8.2)]. Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert dihydrocodeine into its active metabolite, dihydromorphine, more	—

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rapidly and completely than other people. This rapid conversion results in higher than expected serum dihydromorphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Children with obstructive sleep apnea who are treated with dihydrocodeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of dihydrocodeine that has been rapidly metabolized to dihydromorphine [see Use in Specific Populations (8.4)]. SYNALGOS-DC is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)]. When prescribing SYNALGOS-DC, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of dihydromorphine overdose [see Overdosage (10)].	
8 USE IN SPECIFIC POPULATIONS **8.4 Pediatric Use** Preparations containing aspirin should be kept out of the reach of children. Reye's Syndrome is a rare condition that affects the brain and liver and is most often observed in children given aspirin during a viral illness. SYNALGOS-DC is not recommended for patients 12 years of age and under. Since there is no experience in children who have received SYNALGOS-DC, safety and efficacy in children have not been established. Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations).These children may be particularly sensitive to the respiratory depressant effects of dihydrocodeine that has been rapidly metabolized to dihydromorphine. SYNALGOS-DC is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)].	—

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17 PATIENT COUNSELING INFORMATION （略） Ultra-Rapid Dihydrocodeine Metabolizers Advise patients that some people have a genetic variation that results in dihydrocodeine changing into dihydromorphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid dihydrocodeine metabolizer or not. These higher-than-normal levels of dihydromorphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing [see Warnings and Precautions (5.4)]. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. SYNALGOS-DC is contraindicated in all children who undergo tonsillectomy and/or adenoidectomy[see Contraindications (4)]. Advise caregivers of children receiving SYNALGOS-DC for other reasons to monitor for signs of respiratory depression.	—

トラマドール（単剤）

米国　（USPI） ULTRAM tablets (Janssen Pharmaceuticals) 2016 年 12 月改訂	欧州　（EU SmPC） 50/100/150/200 mg, prolonged-release tablets (GRUENENTHAL　GMBH) 2016 年 6 月改訂
INDICATIONS AND USAGE ULTRAM is indicated for the management of pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Limitations of Use Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (see WARNINGS), reserve ULTRAM for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]: ・Have not been tolerated, or are not expected to be tolerated. ・Have not provided adequate analgesia, or are not expected to provide adequate analgesia.	**4. Clinical particulars** **4.1 Therapeutic indications** Treatment of moderate to severe pain
DOSAGE AND ADMINISTRATION **Adults (17 years of age and over)** Important Dosage and Administration Instructions Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (see WARNINGS). Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (see WARNINGS). Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with ULTRAM and adjust the dosage accordingly (see WARNINGS). Initial Dosage *Initiating Treatment with ULTRAM* For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a	**4.2 Posology and method of administration** <u>Posology</u> The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. Daily doses of 400 mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances. Unless otherwise prescribed, <TRADENAME> should be administered as follows: Adults and adolescents above the age of 12 years The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily (see section 5.1). <TRADENAME> should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with <TRADENAME> is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if　necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

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day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day. For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day. *Conversion from ULTRAM to Extended-Release tramadol* The relative bioavailability of ULTRAM compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression. *Dosage Modification in Patients with Hepatic Impairment* The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours. *Dosage Modification in Patients with Renal Impairment* In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of ULTRAM be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, dialysis patients can receive their regular dose on the day of dialysis. *Dosage Modification in Geriatric Patients* In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients over 75 years old, total dose should not exceed 300 mg/day. **Titration and Maintenance of Therapy** Individually titrate ULTRAM to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving ULTRAM to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse (see WARNINGS). Frequent communication is important among the prescriber, other members of the	Paediatric population <TRADENAME> is not suitable for children below the age of 12 years. Older people A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In older people over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements. Patients with renal insufficiency/dialysis and hepatic impairment In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency <TRADENAME> prolonged-release tablets are not recommended.

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healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the ULTRAM dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions. **Discontinuation of ULTRAM** When a patient who has been taking ULTRAM regularly and may be physically dependent no longer requires therapy with ULTRAM, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue ULTRAM in a physically-dependent patient. (see WARNINGS; Drug Abuse and Dependence).	
PRECAUTIONS **Pediatric Use** The safety and efficacy of ULTRAM in patients under 16 years of age have not been established. The use of ULTRAM in the pediatric population is not recommended.	—

トラマドール・アセトアミノフェン（配合剤）

米国 （USPI） ULTRACET tablets (Janssen Pharmaceuticals) 2016 年 12 月 改訂	英国 (UK SPC) Tramacet 37.5 mg/ 325 mg filmcoated tablets (Grunenthal) 2016 年 12 月 19 日 改訂
INDICATIONS AND USAGE ULTRACET is a combination of tramadol hydrochloride, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1) <u>Limitations of Use (1)</u> ULTRACET tablets are indicated for short-term use of five days or less. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve ULTRACET for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]: ・Have not been tolerated, or are not expected to be tolerated. ・Have not provided adequate analgesia, or are not expected to provide adequate analgesia,	**4. Clinical particulars** **4.1 Therapeutic indications** Tramadol hydrochloride/Paracetamol tablets are indicated for the symptomatic treatment of moderate to severe pain. The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see also Section 5.1).
DOSAGE AND ADMINISTRATION ・ Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. ・ Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1) ・ Initiate treatment with two tablets every 4 to 6 hours as needed for pain relief; maximum of 8 tablets per day. (2.2) ・ Do not use with other acetaminophen- or tramadol-containing products. (2, 5.17) ・ <u>Severe Renal Impairment:</u> Do not exceed 2 tablets every 12 hours. (2.3) ・ Do not stop ULTRACET abruptly in a physically dependent patient. (2.4)	**4.2 Posology and method of administration** *Posology* The use of Tramadol Hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol. The dose should be adjusted to intensity of pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total dose of 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day should not be exceeded. The dosing interval should not be less than six hours. <u>Adults and adolescents (12 years and older)</u> An initial dose of two tablets of Tramadol hydrochloride/Paracetamol is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day. The dosing interval should not be less than six hours. Tramadol hydrochloride/Paracetamol should under no circumstances be administered for

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	longer than is strictly necessary (see also section 4.4 Special warnings and precautions for use). If repeated use or long term treatment with Tramadol hydrochloride/Paracetamol is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary. Paediatric population The effective and safe use of Tramadol hydrochloride/Paracetamol has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population. Older patients A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In older people over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements. Renal insufficiency / dialysis In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. Hepatic impairment In patients with hepatic impairment the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements (see section 4.4). Because of the presence of paracetamol Tramadol hydrochloride/Paracetamol should not be used in patients with severe hepatic impairment (see Section 4.3).

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

This is an update to the FDA Drug Safety Communications:

- FDA evaluating the potential risks of using codeine cough-and-cold medicines in children issued on July 1, 2015, and
- FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger issued on September 21, 2015.

Safety Announcement

[4-20-2017] The Food and Drug Administration (FDA) is restricting the use of codeine and tramadol medicines in children. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. We are also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

As a result, we are requiring several changes to the labels of all prescription medicines containing these drugs. These new actions further limit the use of these medicines beyond our 2013 restriction of codeine use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. We are now adding:

- FDA's strongest warning, called a *Contraindication*, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new *Contraindication* to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened *Warning* to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions

in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

Caregivers and patients should always read the label on prescription bottles to find out if a medicine contains codeine or tramadol. You can also ask your child's health care provider or a pharmacist. Watch closely for signs of breathing problems in a child of any age who is taking these medicines or in infants exposed to codeine or tramadol through breastmilk. These signs include slow or shallow breathing, difficulty or noisy breathing, confusion, more than usual sleepiness, trouble breastfeeding, or limpness. If you notice any of these signs, stop giving the medicine and seek medical attention immediately by going to an emergency room or calling 911.

Health care professionals should be aware that tramadol and single-ingredient codeine medicines are FDA-approved only for use in adults. Consider recommending over-the-counter (OTC) or other FDA-approved prescription medicines for cough and pain management in children younger than 12 years and in adolescents younger than 18 years, especially those with certain genetic factors, obesity, or obstructive sleep apnea and other breathing problems. Cough is often secondary to infection, not serious, and usually will get better on its own so treatment may not be necessary.

Codeine and tramadol are a type of narcotic medicine called an opioid. Codeine is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines. Tramadol is a prescription medicine approved only for use in adults to treat moderate to moderately severe pain. However, data show it is being used in children and adolescents despite the fact that it is not approved for use in these patients.

In early 2013, FDA added a *Boxed Warning* to the codeine drug label cautioning against prescribing codeine to children of any age to treat pain after surgery to remove tonsils or adenoids. We also issued Drug Safety Communications in July 2015 and September 2015 warning about the risk of serious breathing problems in some children who metabolized codeine and tramadol much faster to their active form than usual (called ultra-rapid metabolism), causing potentially dangerously high levels in their bodies too quickly. At that time, we said we would continue to evaluate this safety issue. As part of that safety review, the codeine-related safety issues were discussed at an FDA Advisory Committee meeting in December 2015.

Our review of several decades of adverse event reports submitted to FDA* from January 1969 to May 2015 identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. This includes only reports submitted to FDA, so there may be additional cases about which we are unaware. We also identified nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 (see Data Summary). The majority of serious side effects with both codeine and tramadol

occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In our review of the medical literature[1-19] for data regarding codeine use during breastfeeding, we found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature[4,5,23,24] for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

We will continue to monitor this safety issue. We are considering additional regulatory action for the OTC codeine products that are available in some states. OTC codeine products are available in combination with other medicines for cough and cold symptoms. We are also considering an FDA Advisory Committee meeting to discuss the role of prescription opioid cough-and-cold medicines, including codeine, to treat cough in children.

We urge patients and health care professionals to report side effects involving codeine- and tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

List of Prescription Codeine and Tramadol Pain and Cough Medicines

Medicines Containing Codeine	Medicines Containing Tramadol
Codeine Sulfate	Conzip
Butalbital, Acetaminopen, Caffeine, and Codeine phosphate	Ultracet
Fiorinal with codeine	Ultram
Soma Compound with codeine	Ultram ER
Tylenol with codeine	Generic products containing tramadol
Promethazine with codeine (cough)	
Prometh VC with codeine (cough)	
Triacin-C (cough)	
Tuxarin ER (cough)	
Tuzistra-XR (cough)	
Generic products containing codeine	
Medicines Containing Dihydrocodeine	
Synalgos-DC	

Facts about Codeine and Tramadol

- Codeine

    - An opioid pain reliever used to treat mild to moderate pain. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines.
    - Single-ingredient codeine is approved for pain management in adults only.
    - Also used to reduce coughing. It is frequently combined with promethazine in prescription cough-and-cold medicines and with other cold remedies in over-the-counter (OTC) preparations.
    - Common side effects include drowsiness, lightheadedness, dizziness, feeling tired, shortness of breath, nausea, vomiting, stomach pain, constipation, itching, or rash.
    - In 2014, nearly 1.9 million patients 18 years of age and younger received a dispensed prescription for codeine-containing products from U.S. outpatient retail pharmacies. Of the total pediatric patients, nearly 1.4 million patients received codeine-containing analgesic products, and 483,000 patients received codeine-containing cough-and-cold products.[20]
- Tramadol
    - An opioid pain reliever FDA-approved only in adults to treat moderate to moderately severe pain.
    - Available as a single ingredient under the brand names Ultram, Ultram ER, Conzip and also as generics.
    - Also available in combination with acetaminophen under the brand name Ultracet and as generics.
    - Common side effects include headache, dizziness, drowsiness, feeling tired, constipation, diarrhea, nausea, vomiting, stomach pain, itching, or flushing.
    - In 2014, nearly 167,000 patients younger than 18 years of age received a dispensed prescription for tramadol-containing products from U.S. outpatient retail pharmacies. [21]

Additional Information for Caregivers and Patients

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain:
    - Codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years due to the risk of serious side effects, including slowed or difficult breathing and death.
    - Codeine is not recommended to treat cough or pain and tramadol is not recommended to treat pain in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease that may increase the risk of breathing problems.
    - Tramadol should not be used to treat pain in children up to 18 years of age after surgery to remove their tonsils and/or adenoids. The drug label for codeine already warns against use in children up to 18 years of age after surgery to remove their tonsils and/or adenoids.

    - Breastfeeding is not recommended during treatment with codeine or tramadol because the medicine passes through breast milk and can harm the baby.
- Talk to your health care provider or a pharmacist to find out if a medicine your child is taking contains codeine or tramadol.
- Always read the label on prescription bottles to find out if a medicine contains codeine or tramadol, or ask your child's health care provider or a pharmacist.
- If patients of any age are known to be CYP2D6 ultra-rapid metabolizers, which means their bodies convert codeine or tramadol into their active forms faster and more completely than usual, they should not use codeine or tramadol.
- If a child has taken codeine or tramadol and you notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness in a child of any age, seek medical attention immediately by taking the child to an emergency room or calling 911.
- Report any side effects from codeine- or tramadol- containing medicines to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain and requiring the following changes to the drug labels:
    - FDA's strongest warning, called a *Contraindication*, alerting that codeine and tramadol should not be used to treat pain in children younger than 12 years, and codeine should not be used to relieve cough in these children.
    - A new *Contraindication* to the tramadol label to restrict its use in children younger than 18 years to treat pain after a tonsillectomy and/or adenoidectomy. The label of codeine-containing products already carry this Contraindication.
    - A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or compromised respiratory function, that may increase the risk of serious breathing problems.
    - Strengthening the *Warning* to patients that breastfeeding is not recommended during treatment with codeine or tramadol due to the potential for serious adverse reactions in a breastfed infant, such as excess sedation, respiratory depression, and death.
- All tramadol-containing products and single-ingredient codeine drugs are FDA-approved for use only in adults.
- If you have determined that a codeine-or tramadol-containing product is appropriate for an adolescent patient, counsel parents and caregivers on how to recognize the signs of opioid toxicity, and advise them to stop giving the adolescent codeine or tramadol and seek medical attention immediately if their adolescent is exhibiting these signs.

- Report adverse events involving codeine- or tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

Codeine

A search of the FDA Adverse Event Reporting System (FAERS) database from January 1969 to May 2015 identified 64 worldwide cases of respiratory depression, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Fifty cases were reported in children younger than 12 years. Respiratory depression occurred after the children received a range of one to 18 doses, with a median of five doses. The most frequently reported codeine-containing medicines in the cases were acetaminophen with codeine used for pain, and promethazine with codeine (with or without phenylephrine) used for cough and cold.

Of the 24 cases reporting death, 21 occurred in children younger than 12 years. The reasons for codeine-containing medicine use in these cases included post-tonsillectomy and/or adenoidectomy pain management, other post-operative pain, general pain, sore or strep throat pain, and cough and cold.

Ten of the 64 cases mentioned the status of cytochrome P450 isoenzyme 2D6 (CYP2D6) genotype. Seven of these patients were ultra-rapid metabolizers, five of whom died. Ultra-rapid metabolizers of substrates of CYP2D6 convert codeine in their bodies too quickly into potentially dangerously high levels of morphine, the active form of codeine, contributing to life-threatening or fatal respiratory depression. The three other patients were extensive metabolizers, with one death.

Fifteen of the 64 cases reported codeine or morphine blood levels; the remaining 49 cases did not. In 13 cases, the blood levels were above the therapeutic range, and in two cases the blood levels were within the therapeutic range. One patient who had blood levels in the therapeutic range died following pain management post-tonsillectomy and adenoidectomy.

Tramadol

A search of the FAERS database from January 1969 to March 2016 identified nine cases worldwide of respiratory depression in children younger than 18 years of age, including three deaths. With the exception of a 15-year-old treated for multiple days with tramadol, respiratory depression occurred within the first 24 hours of drug administration.

The three fatalities occurred outside the U.S. in children younger than 6 years. Elevated serum tramadol concentrations were noted in all three. The reasons for tramadol treatment in these children were to treat pain after tonsillectomy, pain after clubfoot surgery, and to manage fever. All three cases involved tramadol oral drops, a formulation not available in the U.S.

The one case in which CYP2D6 ultra-rapid metabolizer status was reported occurred in a 5-year-old child from France who was prescribed a single tramadol dose in the evening post-adenotonsillectomy and returned to the healthcare facility the next morning with opioid intoxication; he was resuscitated.[22] A urine sample showed increased metabolite concentrations. Genotyping of CYP2D6 was conducted, and three functional alleles were found that were consistent with ultra-rapid metabolism.

One non-fatal U.S. case involved a 6-year-old who was prescribed tramadol for neuropathy of the hands and feet. After the third dose, the patient experienced respiratory depression and was unresponsive. The patient fully recovered after receiving two doses of naloxone.

Four other non-fatal cases reported in teenagers using tramadol for musculoskeletal pain or sciatica described unresponsiveness or somnolence after one or a few doses of tramadol; all required medical intervention. Two of these were U.S. cases.

Breastfeeding Mothers

Codeine and its active metabolite, morphine, are present in breast milk. A search of the medical literature[1-19] for relevant data regarding codeine use during lactation revealed numerous reports of respiratory depression and sedation, including one infant death, especially in mothers who have the CYP2D6 ultra-rapid metabolizer genotype.

In the case of the infant death, the mother was found to be a CYP2D6 ultra-rapid metabolizer, which potentially led to higher levels of morphine secreted into the breast milk leading to the infant's death. In other studies comparing drowsiness in breastfed babies whose mothers took codeine/acetaminophen compared to acetaminophen alone, the frequency of somnolence was higher in the codeine/acetaminophen-exposed group. Some of the mothers of those babies were CYP2D6 ultra-rapid metabolizers.[15,16]

Mothers who are ultra-rapid metabolizers of codeine achieve higher-than-expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous to their breastfed infants. In women with normal codeine metabolism, the amount of codeine secreted into breast milk is low and dose-dependent.

According to *Drugs in Pregnancy and Lactation*[5], both tramadol and its pharmacologic active metabolite (O-desmethyltramadol) are excreted into human milk. The mean absolute bioavailability of a 100-mg dose is 75%. Thus, ingestion of the recommended dose may produce drug amounts in breast milk that could exceed those reported above. The effect of this exposure on a nursing infant is unknown.

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Related Information

FDA statement from Douglas Throckmorton, M.D., Deputy Center Director for Regulatory Programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers

Consumer Update: Codeine and Tramadol Can Cause Breathing Problems for Children

Use of Codeine and Tramadol Products in Breastfeeding Women – Questions and Answers

Codeine Information

Tramadol Information

Opioid Medications

What's on the Label (high resolution) (PDF - 546KB)

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines

Advisory Committees: Critical to the FDA's Product Review Process

別添 5

1. コデインリン酸塩水和物及びジヒドロコデインリン酸塩（医療用医薬品、一般用医薬品）

呼吸抑制関連（18 歳以下）　国内当局報告症例ラインリスト（4 例）

No.	医薬品の種類（医療用/一般用）	年齢	性別	副作用（PT）	転帰
1	医療用	10 歳未満	不明	チアノーゼ 呼吸困難	不明
2	医療用	10 歳未満	不明	呼吸抑制	不明
3	一般用	10 歳未満	女性	急性呼吸不全	回復
4	一般用	10 歳未満	女性	各種物質毒性	後遺症

2. トラマドール

該当する副作用報告はなかった。