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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Ricinus communis* L., oleum

Draft

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Ricinus communis* L., oleum (castor oil)
Herbal preparation	Fatty oil obtained from seeds of *Ricinus communis* L. by cold expression
Pharmaceutical forms	Herbal preparation in liquid or solid dosage forms for oral use
Rapporteur	C. Purdel
Peer-reviewer	B. Kroes

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Ricinus communis* L., oleum. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/☐contact

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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance

The HMPC has established a European Union herbal monograph on the oil obtained from the seeds of *Ricinus communis* L., fam. Euphorbiaceae. The monograph does not cover the herbal substance itself, i.e. the seeds.

- Herbal preparations

Ricini oleum virginale (virgin castor oil) is the fatty oil obtained by cold expression of the seeds of the plant *Ricinus communis* L. (Euphorbiaceae family), in accordance with the European Pharmacopoeia (01/2013:0051). The addition of a suitable antioxidant is accepted. As specific requirements, during the expression step, the temperature of the oil must not exceed 50^0C.

The European Pharmacopoeia includes another two monographs: *Ricini oleum raffinatum* (01/2013:2367) that represents refined castor oil which may contain a suitable antioxidant and *Ricini oleum hydrogenatum* (01/2008:1497) that represent fatty oil obtained by hydrogenation of virgin castor oil.

Definitions, production and labelling requirements for vegetable fatty oils are given in the general monograph in the European Pharmacopoeia.

Castor oil is extracted from the seeds from Ricinus communis (that contain 42-55% fatty oil) by: (1) the use of a solvent or (2) by mechanical crushing, grinding, and pressing. The cold expression method is more efficient, leaving a more desiccated residue (**Cosmetic Ingredient Review Expert Panel, 2007**). According to Ph.Eur monograph only the oil obtained by cold expressing is accepted.

- Constituents

Chemically, castor oil is a mixture of triglyceride characterized by a high content of ricinolein (a glyceride of 12-hydroxy-9-octadecenoic acid). Many publications reported ricinoleic acid as the major component in castor oil: 89.2-94.9% (**Gupta *et al.,* 1951**), about 70-90% (**Foglia *et al.*, 2000**), 87-90% (**Puthli *et al.,* 2006**), over 89% (**Ogunniyi *et al.,* 2006**) and 90.2% (**Conceicao *et al.,* 2007**).

Beside ricinoleic acid, other fatty acids are present in castor oil, like linoleic acid (4-5%), oleic acid (2-3%), palmitic acid, stearic acid, dihydroxystearic acid (each 1%), and trace amounts of other fatty acids (**Stübiger *et al.,* 2003**).

According to the European Pharmacopeia, castor oil should contain max. 2.0% palmitic acid, max. 2.5% stearic acid, 2.5-6.0% oleic acid and isomers, 2.5- 7.0% linoleic acid, max. 1.0% linolenic acid, max. 1.0% eicosenoic acid, 85.0-92.0% ricinoleic acid and max. 1.0% any other fatty acid (Ph. Eur. 01/2013:0051 and Ph. Eur. 01/2013:2367).

Other sources mention that castor oil also contains 2.4% lauric acid lipase, vitamin E, and *β*-sitosterol (**Cosmetic Ingredient Review Expert Panel, 2007**).

A lectin called ricin is present in the seeds and pods and is considered as one of the most toxic natural poisons. It is a glycoprotein composed of two polypeptide chains, the A-chain (30 kDa) and B-chain (32 kDa), linked with a disulfide bond and with a molecular weight of about 63,000. Reported ricin content in the castor bean varies between 1% and 5%. After isolation of the oil, ricin remains in the

bean pulp therefore the castor oil is not considered to contain ricin (**Worbs et al., 2011**). Also Cosmetic Ingredient Review Expert Panel (2007) published a safety assessment that stipulates that castor oil does not contain ricin.

Ricinine (1,2-dihydro-4-methoxy-1-methyl-2-oxo-3-pyridinecarbonitrile) is a piperidine alkaloid present in small amounts in the castor bean (0.3-0.8%) and leaves, but not in castor oil (**Bruneton, 2005**).

Castor oil, virgin and refined According to the monographs from European Pharmacopoeia the composition of the fatty-acid fraction of the oils is identical: palmitic acid (max. 2.0%), stearic acid (max. 2.5%), oleic acid and isomers (2.5-6.0%), linoleic acid (2.5-7.0%), linolenic acid (max. 1.0%), eicosenoic acid (max. 1.0%), ricinoleic acid (85.0-92.0%) and any other fatty acid (max. 1.0%).

Comparing the monographs, the appearance, the specific absorbance, the acid and peroxide values are different. The other parameters are identical.

Table 1: Comparative parameters castor oil virgin vs. refined

Parameters	**Castor oil virgin** (01/2013:0051)	**Castor oil refined** (01/2013:2367)
Appearance	Clear(at 40^0C), slightly yellow, viscous, hygroscopic liquid	Clear, almost colourless or slightly yellow, viscous, hygroscopic liquid Viscosity: about 1000 mPas
Specific absorbance	Max. 0.7	> 0.7 and < 1.5
Acid value	Max. 1.5	Max. 0.8
Peroxide value	Max. 10.0	Max. 5.0

The Quality Drafting Group of the HMPC is of the opinion that virgin castor oil and refined castor oil are comparable because the refining process affects impurities only, which means that active ingredients are not changed by the process. The difference in impurity content has no implications to safety and efficacy. Consequently the European Union herbal monograph covers both oils and no distinction is made between the virgin and refined castor oil in this assessment report.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Search and assessment methodology

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on castor oil or its relevant constituents:

- Relevant articles and references retrieved from databases: PubMed and Toxline. Search term: [Ricini oleum], [Castor oil], [Ricinus communis] and [Ricinus communis oil]. Publication year: up to April 2014. In summary 1800 publications were listed.
- Textbooks, pharmacopoeias and monographs.

Additionally, the European Commission´s databases on cosmetic ingredients (CosIng) was searched in April 2014 for information on [castor oil].

Data was also provided by the EMA on behalf of interested parties.

The EudraVigilance database and VigiLyze database of the World Health Organization's were searched in August 2014 using the term [Ricini oleum].

The abstracts of the references found were screened manually and all articles identified that could have a possible impact on the assessment report and monograph were included. This assessment report is based on the summary of the most relevant scientific literature.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 2: Overview of data obtained from marketed medicinal products.

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status (date, Member State)**
Castor oil	Functional constipation not corrected by diet.	Oral liquid. For internal use: for children 1 to 5 years old: 5 ml once a day, for children 5 to 12 years old: 10 ml once a day, for adolescents, adults, in elderly: 15-30 ml once a day. The use in children under 1 year of age,is not recommended. Duration of use:	Since 17.08.2001, Estonia, WEU

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		maximum 3 days	
Castor oil, refined	Short-term use in cases of constipation.	capsule, 1000 mg >12 years: 1-10 capsules 1 time daily in the morning no longer than 2 weeks	at least since 1976, DE, WEU
Castor oil, virgin	Short-term use in cases of constipation.	capsule 500 mg >12 years: 2-20 capsules, soft 1 time daily in the morning no longer than 2 weeks	at least since 1976, DE, WEU
Castor oil	In constipations due to various reasons.	Oral liquid 100% children in the age of 12 y 1-2 teaspoons (4-8g). adults 1-2 spoons (12-24g) designed for temporary use	since 11/04/2011, Poland, TUR**
Castor oil	Functional constipation. Clearing of bowels before radiological examination, surgery, labour.	Oral liquid. posology: children 1-5 years old: 1 teaspoon (5 g) children: 5-12 years old: 1 desert spoon (10 g) adults and elderly: 1-2 spoon (15-30 g)	since 1998, Latvia, WEU Note: On the market of former Soviet Union at least since 1967***
Castor oil BP 100%	Laxative	Oral liquid. posology: children up to one year: ten drops 1-12 years: ten drops to two (5 ml) spoonfuls according to age. adults and elderly: one to four (5 ml) spoonfuls to be taken in milk or lemon juice one hour before breakfast or on an empty stomach.	Since 28.09.1989, UK****

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Castor oil	Traditionally used as a purgative	Oral liquid Adolescents and adults: Single dose: 30 ml, in the morning	France from 1959 to 2011, TUR

** **Additional data on other products marketed in Poland**: In Poland castor oil was used with a similar indication in 24.06.1938 (Regulation of Minister of Health and Social Welfare). After the II-nd World War it was mentioned by management of the Minister of Health and Social Welfare in 24.02.1958 (in forms of oral liquid and capsules). In 28.01.1960 it was accepted for distribution in drugstores and herbalistic shops. In 14.09.1993 it was exempted from registration (a category similar to magistral drugs) and all products started to be certified by the Drug Institute. According to available databases the Certificates of Registration were given for 9 products. 8 products are now on the pharmaceutical market in Poland, one as TUR.

*** Additional information provided by Latvia demonstrated that castor oil was on the market in the former Soviet Union since 1967

**** data collected from MHRA site; Additional data from UK indicate that the product has been authorised before 1968 as WEU, but the license was withdrawn in 2013, taking into account that castor oil is considered obsolete as laxative in UK.

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable.

Information on other products marketed in the EU/EEA (where relevant)

Not applicable.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

The castor oil plant *Ricinus communis*, also known as *Palma(e) Christi* or wonder tree, is a perennial scrub of the spurge family *Euphorbiaceae*. *Ricinus communis* is probably native to eastern Africa and was used in ancient Egypt and by the Romans and Greeks (**Williamson, 2003**). Nowadays the plant grows wild in many tropical and subtropical regions and is found as an ornamental plant virtually all around the world.

A companion to the British Pharmacopoeia 3rd edition, published in 1866 describes castor oil properties as "*a mild and speedy cathartic. Particularly applicable to constipation from indurate faeces, or after swallowing acrid substances, or on the accumulation of acrid secretions. Used in diseases attended*

with irritation or inflammation of the bowels, as colic, diarrhoea, dysentery, and enteritis". Dose administered corresponds 1/2 to 1 oz. for adults, 1 to 3 drms. (meaning ml) for infants. The oil is administered floating on some aromatic water, or mixed in a cup of hot sweetened coffee (**Squire, 1866).**

According to Potter's Herbal Cyclopaedia, castor oil has been used since ancient times as a laxative and purgative. The authors do not recommend regular use and for long periods because the oil is believed to cause histological abnormalities in the intestine. Castor oil is also emollient and soothing to the skin and eye and is an ingredient of many cosmetic and ophthalmic preparations. The dosage indicated for oral intake corresponds to 5-20 ml **(Williamson, 2003)**

Some old medical journals described castor oil as a very potent agent producing catharsis by irritation. Because of this property, the author recommended not to use the oil for the treatment of functional constipation (**McKenna, 1964**). Other journal (California and Western medicine, 1934) describe the use of castor oil for the induction of labor (**Holmes, 1934**)

In 'Precis de Matiere Medicale', castor seeds but also four castor oil types (huile de premiere pression; huile pharmaceutique; huile de la deuxieme pression; huile sulfuree) are described. As therapeutic indications, the internal use of 30-50 g (in adults) and 10-15 (in children) have purgative effect. It is described that 10-30 g induce an effect after 3-4 hours, while 30-50 g may have an effect whithin 5 to 6 hours, without any intestinal irritation (**Leurier et al., 1946**).

In Handbuch der Pharmacognosie a short history of castor oil and the description of method of preparation of medicinal and technical castor oil are included (**Tschirch, 1923**).

Ożarowski et al. (1978) included castor oil in a textbook *(Lekiroslinne informator*), indicating its use in constipations or due to various reasons (including food poisoning, intestinal infections, after use of anthelmintics, before radiological examinations).

British Pharmaceutical Codex 1979 includes 5 preparations based on castor oil, of which 3 used internal as purgative: *Emulsio Olei Ricini Aromatici*, that contains 30% (v/v) of aromatic castor oil and is administered in dose of 30 to 60 ml; *Mistura Olei Ricini*, that contains castor oil emulsified with acacia in triple orange-flower water and cinnamon water; Dose (as a single draught)-30 to 60 ml and Oleum Ricini Aromaticum (that contains castor oil, flavoured with saccharin, vanillin, chloroform and oils of cinnamon, clove and pimento and is administered in dose of 4 to 30 ml).

Martindale, The Extra Pharmacopoeia (1982) indicates that castor oil is a purgative acting on the small intestine, the latency until the effect vary between 2 and 8 hours. It is also given at dose of 15 ml to empty the bowel before X-ray examination. Externally is an emollient, used in preparations such as Zinc and castor oil ointment (**Reynolds, 1982**).

Dobrescu et al. (1989) mentions that virgin castor oil is apurgative that is administered in acute constipation in a single dose of 15-30 g in adults and 5-15 g in children more than 2 years old and 1-5 g in children that are less than 2 years old.

Also the Romanian Pharmacopoeae X (1998) and Farmakopea Polska IV (1970) include the monograph of "Ricini oleum" with the indication as purgative drug. The single dose in adults corresponds to 5-30 g (in Romania) and to 5-20 g (Poland).

WHO monograph describes for Oleum Ricini traditional medicinal uses as emenagogue, to induce labor, for the treatment of burns, haemorrhoids, pneumonia, rheumatism and sprains and well-established medicinal uses as short-term treatment (3-5 days) for acute constipation when other dietary methods of bulk-forming laxatives have not provided adequate relief. As a cathartic for use in bowel evaluation

prior to surgery or for external use for topical dermatoses and dermatitis. The dose indicated as laxative is 1-10 ml, as single daily dose, while for induction of labour: 4-60 ml as maximum single dose, under medical supervision is indicated (**WHO, 2009**).

PDR for Herbal Medicine also included castor oil as drug used internally in folk medicine for acute constipation, in intestinal inflammation, for removal of worms, and as a form of birth control. The oil is used externally for inflammatory skin disorders, furuncles, carbuncles, abscesses, inflammation of the middle ear and headaches (poultice). Recommended oral daily for acute constipation or as laxative against worms is, at least] 10 grams divided 1 or 5 doses, while for external use, a paste made of grounded seeds is applied to the affected skin areas twice daily, up to 15 days (**Grunewald *et al.,* 2004**).

Table 3: Overview of historical data

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Reference**
Castor oil	Laxative Induction of labour under medical supervision	a) Oral use: single daily dose of 1-10 ml b) Oral use: maximum single dose of 4-60 ml	WHO monograph, vol.4, 1997
Castor oil	a) Internally, for acute constipation, intestinal inflammation, for removal of worms b) Externally for inflammatory skin disorders, furuncles, carbuncles, abscesses, inflammation of the middle ear and headaches(poultice)	a) At least 5(x 2 g)or10(x 1 g) capsules must be taken b) A paste made of ground seeds is applied to the affected skin areas twice daily. A course of treatment takes up to 15 days	Gruenwald *et al.,* 2004
Castor oil BP	Laxative and purgative	Oral liquid: 5-20 ml	Williamson, 2003
Ricini oleum	In constipations or due to various reasons (including food poisoning, intestinal infections, after use of anthelmintics, before radiological examinations).	Oral liquid: 5-20 g	Farmakopea Polska IV
Castor oil	Purgative	Oral liquid: 5-20 g (in adults)	Romanian Pharmacopoeia, IX and X
Castor oil	As purgative(internal use).	Oral liquid: 30-50 g (in adults); 10-15 g (in children)	Leurier *et al*., 1946
Virgin castor oil	As purgative in acute constipation.	Oral liquid A single dose of 15-30 g in adults and 5-15 g in children > 2 years old and 1-5 g in children < 2 years old.	Dobrescu *et al*., 1989

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
a) Emulsio Olei Ricini Aromatic b) Mistura Olei Ricini c) Oleum Ricini Aromaticum	Purgative	a) 30 - 60 ml b) 30 - 60 ml c) 4 - 30 ml	British Pharmaceutical Codex, 1979
Castor oil	Purgative	15 ml	Reynolds,1982

2.3. Overall conclusions on medicinal use

From market overview (section 2.1) the following indications and respective herbal preparations were identified:

In UK (WEU): As laxative - since 1968

In Germany (WEU): Short-term use in cases of constipation - since 1976

In Estonia (WEU): Functional constipation not corrected by diet - since 2001

In Latvia (WEU): Used in functional constipation. Clearing of bowels before radiological examination, surgery, labour - since 1998 (and since 1967 in former Soviet Union)

In Poland: Traditionally used in constipations since 2011 as TUR and since 1985 with certificate of registration.

In France: Traditionally used as a purgative since 1959

Based on available clinical literature, information provided by Member States and taking into account HMPC opinion, the following indication is recommended for well-established use:

Laxative for short-term use in cases of occasional constipation

Based on clinical trails performed the following posology is proposed:

In adolescents, adults and elderly:

Single dose: 2-5 g (2,1-5,3 ml); in the morning

Duration of use: 7 days

The medicinal use of castor oil (virgin and refined) is documented in several medicinal handbooks throughout a period of at least 30 years, including at least 15 years within the EU.

Castor oil is authorized in the European Union for cleaning of the bowels since 1959 and as a laxative since 1968. Based on this longstanding use and available clinical data just one well-established use indication is proposed in the monograph.

The use of castor oil in children and adolescents under 18 years of age is not recommended due to lack of adequate efficacy and safety data.

Table 4: Overview of evidence on period of medicinal use.

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Virgin Castor oil	Short-term use in cases of constipation.	Herbal preparation in solid dosage form for oral use. oral use. adolescents, adults and elderly: 1-10 g, one time daily in the morning	since 1976 in Germany
Refined castor oil	Short-term use in cases of constipation.	Herbal preparation in solid dosage form for oral use. oral use. adolescents, adults and elderly: 1-10 g, one time daily in the morning	Since 1964 in Germany
Castor oil	Laxative	Herbal preparation in liquid dosage form for oral use. oral use. children up to one year: ten drops; 1-12 years: ten drops to 10 ml according to age. adults and elderly: 5-20 ml, single dose, in the morning	since 1968 in UK
Castor oil	Clearing of bowels before radiological examination or surgery.	Herbal preparation in liquid dosage form for oral use. oral use. adolescents, adults and elderly: single dose: 15-30 g	since 1998, Latvia, WEU
Castor oil	In constipations due to various reasons (including food poisoning, intestinal infections, after use of anthelmintics, before radiological examinations).	Herbal preparation in liquid dosage form for oral use. oral use. children in the age of 12 y: single dose: 4-8 g adults: single dose: 12-24 g	since 11/04/2011, Poland, TUR (actually since 1995)
Castor oil	Functional constipation not corrected by diet.	Herbal preparation in liquid dosage	since 17.08.2001,

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
		form for oral use. Children 1 to 5 years old: 5 ml single dose Children 5 to 12 years old: 10 ml single dose Adolescents, adults, in elderly – 15-30 ml, single dose	Estonia, WEU
Castor oil	Traditionally used as a purgative	Herbal preparation in liquid dosage form for oral use. Adolescents and adults, 30 ml, single dose	Since 1959, France TUR

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

Castor oil is an anionic surfactant laxative. Orally ingested castor oil is hydrolyzed in the small intestine by pancreatic lipases to yield glycerol and ricinoleic acid. Ricinoleic acid acts as a local irritant resulting in electrolyte secretion in the small intestine by reducing net absorption of fluid and electrolytes and stimulates intestinal peristalsis (**Brunton *et al.,*** 1990). Gross morphological damage to the intestinal mucosa arising from the potency of this surfactant action may explain, in part, the altered permeability caused by castor oil (**Cline *et al*.,** 1976).

Because ricinoleate acts in the small intestine, accumulation of fluid and evacuation takes place within 1–6 hours, and it continues until the compound is excreted via the colon. Colonic emptying is so complete that several days may elapse before a normal bowel movement occurs (**Gaginella and Phillips, 1976).**

There are several non-clinical studies conducted in ricinoleic acid, the active ingredient of the castor oil and on sodium ricinoleate *in vitro* **(Cline *et al*., 1976 Racusen and Binder, 1979**) and *in vivo* (**Mathias *et al*., 1978; NTP, 1992**).

Today, castor oil-induced diarrhoea is a standard method used in animal tests to investigate anti-diarrhoeal effect of some compounds, since it allows the observation of measurable changes in the number of stools and intestinal content volume (**Ezeonwumelu *et al.,* 2012**).

In vitro experiments

Castor oil:

Mathias *et al.* (1978) examined the myoelectric effects of castor oil, ricinoleic acid (cis isomer) and ricinelaidic acid (trans isomer) in the small intestine of New Zealand white rabbits. Ricinoleic acid, 2 *µ*g/kg/min (6 mM), was directly perfused into a distal 12-cm ileal loop.

An abnormal myoelectric pattern developed that was similar to the alteration in the electrical activity that has previously been reported for cholera enterotoxin. Castor oil at 0.85 ml/kg, had a similar effect, while ricinelaidic acid had no activity. A second preparation consisted of an intraluminal perfusion of ricinoleic acid, 2 *µ*g/kg/min into the first section of the duodenum. The abnormal myoelectric pattern was observed in the jejunum and the ileum but not the duodenum. The mean onset time for the development of this altered myoelectric state for all experiments was 3.5 h. According to the authors these results suggest that an active motility component in addition to the secretory state exists throughout the small intestine that is exposed to castor oil or ricinoleic acid. The biopsy of the ileal loops at the end of each experiment revealed no alteration in intestinal structure.

Isolated compounds:

Stewart *et al.* (1975) investigated the effects of ricinoleic acid and several structurally related compounds on the smooth muscle contractions of the coaxially stimulated guinea-pig ileum, the spontaneously contracting rabbit jejunum, 90 mM potassium depolarized guinea-pig taenia coli and rat colon. In concentrations of 1.25 x 10^{-5} to 4 x10^{-4} M, ricinoleate produced a dose-dependent depression of the stimulated guinea-pig ileum. This action was not produced by matching concentrations of oleate, elaidate, linoleate, 12-hydroxystearic acid, 10(9)-hydroxystearate, the methyl ester of ricinoleic acid or the trans isomer, ricinelaidate. The alcohol derivative, ricinoleyl alcohol, was active and, although the depression produced by it took longer to maximize, the dose-response curves for ricinoleate and ricinoleyl alcohol on this tissue were almost superimposable. Ricinoleate showed the same qualitative and quantitative effects on the spontaneously contracting rabbit jejunum, but several differences were noted on the depolarized preparations. Ricinoleate-induced depression of depolarized smooth muscle was much slower in onset and required about 10 times higher concentrations to achieve equivalent responses. The effect was slowly reversible after several washes with drug-free bath solution. According to the authors these results show that ricinoleic acid is not a stimulant or irritant to isolated intestinal smooth muscle.

Racusen and Binder (1979) investigated the effect of sodium ricinoleate on isolated rat colonic mucosa. 0.5 mM Na ricinoleate perfusion produced significant fluid accumulation, a significant decrease in net Na absorption from 4.7+0.8 to 0.1+0.7 µeq/h cm^2 and reversed net Cl transport from absorption (+4.5±0.9) to secretion (-2.2+0.8 µeq/h cm^2). In parallel studies 0.5 mM Na ricinoleate increased mucosal cyclic AMP content by 58%.

Cline *et al.* *(*1976 investigated *in vivo*, in perfused hamster small intestine the effect of sodium ricinoleate. A concentration of ricinoleate (2 mM) which did not affect water transport, however, did not alter intestinal permeability. At 8 mM ricinoleate induced intestinal secretion (effect on water and sodium), which was accompanied by substantial architectural mucosal changes: mucosal cell exfoliation, villi were shortened and villus tip epithelial cells were vacuolated with disintegrating brush borders.

Gadacz *et al.* *(*1976) investigated on perfused isolated segments (jejunal and ileal Thiry-Vella loop) from dogs the effect of ricinoleic acid. The perfusion with 5 mM ricinoleic acid reduced fluid absorption, compared with the control solution. Perfusion of one loop with ricinoleic acid produced no changes in fluid absorption from the loop perfused with the control solution.

Stewart and Bass (1976) administered intraduodenally oleic and ricinoleic acids or their trans isomers, elaidic and ricinelaidic acids, and evaluated their effects on the digestive motor activity of the

canine small and large bowel. Administration of each cis fatty acid produced an initial stimulation in jejunal areas of about a 2-min duration followed by a post-stimulatory inhibition. Both the initial stimulation and post-stimulatory inhibition were greater for ricinoleic acid than for oleic acid. Minimal or no effects were produced in ileal or colonic areas. In contrast, the trans isomers produced little or no effect on either the small or large bowel. Alterations in the digestive contractile patterns produced by oral administration of 10 ml of oleic, ricinoleic acid or their respective triglycerides were also tested. Ricinoleic acid and castor oil produced a brief initial stimulation followed by prolonged inhibition of small bowel motor activity. The authors classify the laxative effect of both cathartics as mild. Digestive motor patterns returned to control approximately 45 min after oleic acid. There was no indication at any time of an initiation of continuous contractile activity after ricinoleic acid or castor oil which could justify the use of the terms irritant of stimulant to describe their actions.

Gaginella *et al.* (1977) investigated the morphology of the rabbit colon after perfusion of the organ with 2.5, 5.0, 7.5, and 10 mM sodium ricinoleate. Colons perfused with ricinoleate produced desquamation of surface epithelial cells. Surface changes in the colon were comparable with those reported after similar treatment of the rabbit ileum. Concomitant with these histological changes was loss of DNA into the lumen of the colon. Dose-related changes in net fluid transport and mucosal permeability (as assessed by lumen to plasma flux of low molecular weight polyethylene glycols and plasma to lumen flux of urea and creatinine) were also associated with ricinoleate perfusion.

Beubler and Juan *et al*. (1979) observed that ricinoleic acid, oleic acid, sennoside A + B and mannitol reduced or reversed water flux from lumen to blood in rat colon in situ. Ricinoleic acid, oleic acid and sennoside A + B stimulated release of PGE-like material into the colonic lumen whereas the osmotic laxative mannitol and stearinic acid did not. Inhibition of PGE biosynthesis by pretreatment of the rats with indomethacin significantly reduced (but did not abolish) the effect of ricinoleic, oleic and deoxycholic acids on net water flux and PGE release. The amount of PGE release in experiments with ricinoleic acid, oleic acid and stearinic acid (with and without indomethacin) showed a good correlation ($r = 0.99$) with the change in net water flux.

JECFA monograph cites a study where sodium ricinoleate at 2 mM concentration caused a 48% reduction in net water absorption *in vitro* by isolated segments of hamster jejunum. The substance also caused a significant decrease in sodium and chloride absorption, but not potassium absorption **(JECFA, 1979)**

In vivo experiments

Castor oil

NTP cites a gavage study on rhesus monkeys (1 ml/kg castor oil, daily for 4 days) that caused mild morphological changes in the small intestine, characterized by lipid droplets along the mucosal epithelium and in the underlying lamina propria (**NTP, 1992**).

Atchison *et al.* (1978) investigated the effects of castor oil and ricinoleic acid on small bowel electrical activity in the fasted conscious dog and were compared to the effects elicited by two non-laxative oils (triolein and oleic acid). 40 ml of either castor oil, triolein, ricinoteic acid, or oleic acid was administered by gastric tube, and electrical recordings monitored for the next 2 hr. Spike potential activity was monitored at two jejunal sites usingunipolar recording electrodes. The oral administration of 40 ml of castor oil and ricinoleic acid produced catharsis in all animals tested. The onset of watery stools occurred either toward the end of the 2-hr experimental period or shortly thereafter. Castor oil, ricinoleic acid, and triolein produced an increased incidence of basic electrical rhythm (BER) with associated spike potentials when compared to a fasted control; however, the total electrical spiking activity produced by these oils was not statistically different from that induced by feeding. No

treatment altered any of the characteristics of BER. A novel pattern of electrical spiking activity was observed in response to the laxatives. This pattern consisted of short repetitive bursts of spike potentials which migrated the length of the recording site. The laxative-induced electrical pattern persisted for several days after electrical activity resumed within 24 hr. The laxative-induced electrical pattern was shown to be quantitatively distinct from those produced by feeding, fasting, or non-laxative oils.

Isolated compounds

In a study by **Morehouse *et al*.** (1986), a single 0.1 ml dose of ricinoleic acid (100 mg/ml) administered intragastrically to fasted CD-1 mice produced significant alterations in the proximal small intestinal mucosa. At 2 h post dosing, the duodenal villi were markedly shortened when compared to control duodenal villi. This erosion of the villi throughout the duodenum caused massive exfoliation of columnar and goblet cells, filling the lumen with cellular debris and mucus. Disruption of the mucosal barrier resulted in continuity between the intestinal lumen and lamina propria of the villi, with the loss of formed blood elements and lamina propria constituents into the intestinal lumen. The mucosal damage was much more localized at 4 h post dosing, and the erosion of the villi had been largely repaired. Repair was complete at 6 h post dosing.

Table 5: Overview of the main non-clinical data- studies on gastrointestinal motility and water absorption

Herbal preparation tested/ Isolated compounds	**Strength/ Concentration Dosage Route of administration**	**Experimental model** ***In vivo/ In vitro***	**Reference Year of publication**	**Main non-clinical conclusions**
Ricinoleic acid	0.1 ml of ricinoleic acid (100 mg/ml), single dose, oral gavage	*In vivo*	Morehouse *et al*., 1986	Erosion of the villi throughout the duodenum and massive exfoliation of columnar and goblet cells, filling the lumen with cellular debris and mucus.
Ricinoleic acid	1 ml/kg/day, 4 days, oral	*In vivo*	NTP, 1992	Mild morphological changes in the small intestine, characterized by lipid droplets along the mucosal epithelium and in the underlying lamina propria.
Ricinoleic acid	5 mM	*In vitro*	Gadacz, 1976	Loops perfused with ricinoleic acid showed reduced fluid absorption.
Ricinoleic acid	1.25×10^{-5} to 4×10^{-4} M	*In vitro*	Stewart *et al*., 1975	Depressed the spontaneous or induced contractile activity of isolated intestinal smooth muscle preparations.
Sodium ricinoleate	2 and 8 mM	*In vivo*	Cline *et al*., 1970	Induced intestinal secretion (effect on water and sodium) and architectural changes

Herbal preparation tested/ Isolated compounds	**Strength/ Concentration Dosage Route of administration**	**Experimental model** ***In vivo/ In vitro***	**Reference** **Year of publication**	**Main non-clinical conclusions**
				(mucosal cell exfoliation).
Sodium ricinoleate	2 mM	*In vitro*	JECFA, 1979	48% reduction in water absorption and a significant decrease in Na^+ and Cl^- absorption.
Sodium ricinoleate	0.5 mM	*In vitro*	Racusen *et al*., 1979	Fluid accumulation, significantly decreased Na^+ absorption and reversed Cl^- transport from absorption to secretion.
Sodium ricinoleate	0, 2.5, 5.0, 7.5 or 10.0 mM	*In vitro*	Gaginella *et al*., 1977	A dose-related epithelial damage and increases in mucosal permeability.
Castor oil	10 ml, by stomach tube	*In vivo: dogs*	Stewart *et al*., 1976	Decreased the activity of circular smooth muscle in the intestine.
Castor Oil and ricinoleic acid	Castor oil (0.85 ml/kg) into the oral end of the ileal loop ricinoleic acid (2 µg/kg/min) into the oral end of the ileal loop/or intraluminal perfusion	*In vitro*	Mathias *et al*., 1978	Castor oil and ricinoleic acid induced abnormal myoelectric activity (in the jejunum and ileum but not in duodenum).
Castor oil and ricinoleic acid	40 ml of castor oil, or ricinoteic acid, by gastric tube	*In vivo*	Atchison *et al*., 1978	Produced catharsis and abnormal electrical spiking activity.

Mechanism of action

Gaginella *et al*. *(*1977) used electron microscopy to investigate the effect of sodium ricinoleate (10 mM) on mucosal structure of the small intestine of rabbit. Sodium ricinoleate produced deep clefts or holes at the tips of villi and at the bases of these clefts unusual cells could be resolved. The microvillus surface of the intestine was also altered at the tips and sides of villi. Microvilli were clumped into "tufts" with numerous intervening "cracks" appearing on the surface. The appearances after ricinoleate were reversed in part during perfusion with control buffer for 2 hr. The authors concludethat these changes may be related to the well-documented capacity of ricinoleate and dietary long-chain fatty acids to evoke fluid secretion in the intestine.

Gaginella *et al.* (1976) investigated *in vitro* on isolated epithelial cells from hamster small intestine the cytotoxicity of castor oil and other intestinal secretagogues. Cytotoxicity was assessed by: 1) exclusion of trypan blue; 2) release of intracellular (prelabeled) 51Cr; and 3) inhibition of cellular uptake of 3-O-methylglucose. Ricinoleate produced a dose-dependent (0.1-2.0 mM) cytotoxicity as assessed by all three methods. Oleic acid was less potent. The dihydroxy bile acid, deoxycholate, was

equipotent with ricinoleate but its trihydroxy-congener, cholate, was less potent. Dioctyl sodium sulfosuccinate had cytotoxicity similar in magnitude to that of ricinoleate and deoxycholate.

Capasso *et al*. (1984) studied the effect of ricinoleic acid on prostaglandin E2 (PGE2)-evoked contractions on guinea-pig isolated ileum. Addition of ricinoleic acid (10 µg/ml) to the organ bath increased the amplitude of the PGE2-evoked responses. Ricinoleic acid (10 µg/ml) also sensitized the guinea-pig isolated ileum to acetylcholine and histamine. The effect of the ricinoleic acid was reduced by indomethacin either in-vivo (10 µg/ml) or in-vitro (2 µg/ml).

Tavares *et al.* (1996) compared the effect of rhein and aloe-emodin with ricinoleic acid and calcium ionophore A23187 on platelet-activating factor (PAF) release by human gastrointestinal mucosal pieces in vitro. Ricinoleic acid and calcium ionophore stimulated release of PAF from human stomach, ileum or colon mucosa. Aloe-emodin (100 µg/ml) stimulated a small release of PAF in ileum and colon mucosa. Rhein had no effect. 5-Aminosalicylic acid (100 µg/ml) inhibited PAF release induced by the drugs.

The effects of NG-nitro-L-arginine methyl ester (L-NAME) and NG-monomethyl-L-arginine (L-NMMA), inhibitors of nitric oxide (NO) synthase, were studied by **Izzo *et al.*** (1993) on ricinoleic acid-evoked contractions in rat isolated ileum. Ricinoleic acid (10^{-5} to 10^{-4} M) caused a concentration-dependent contraction. Addition of L-NAME (30-300 microM) or L-NMMA (30-300 microM) to the Tyrode's solution increased in a concentration-dependent fashion the amplitude of the ricinoleic acid-evoked responses. L-Arginine (900 microM), a natural substrate of NO synthase, but not D-arginine (900 microM), counteracted the effect of L-NAME (300 microM). The potentiating effect of L-NAME was also prevented by sodium nitroprusside (0.1-1 microM), a generator of NO. According to the authors, these results provide evidence that endogenous NO may modulate the contraction of rat ileum induced by ricinoleic acid.

Later published articles (**Mascolo *et al.,* 1994, Capasso *et al.,* 1994**) confirmed that castor oil (2 ml/rat, orally) induced diarrhea in rats and that this effects involves the L-arginine nitric oxide pathway. Macroscopic damage produced by castor oil (2 ml/rat) throughout the duodenum and jejunum was mild by 1 h, severe 3 and 5 h after castor oil administration and less severe 7 h after challenge. No injury was observed at 0.5 h or at 9 h after castor oil administration and the tissue appeared normal by visual examination (**Mascolo *et al*., 1994**).

Recently, **Tunaru *et al.*** (2012) identified prostaglandin E2 receptors as targets of ricinoleic acid and show that the EP3 receptor mediates *in vivo* the effects of castor oil on the motility of the uterus and the intestine in genetic mouse models.

3.1.2. Secondary pharmacodynamics

No relevant data available.

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

The scientific literature contains numerous non-clinical pharmacological studies on ricinoleic acid and less on castor oil. Ricinoleic acid is the active metabolite of castor oil. It is formed in the small intestine by pancreatic lipase. Therefore, the results obtained with this Ricinoleic acid also support the proposed indication. The mechanisms underlying the pharmacological effects of ricinoleic acid remain elusive. Several studies have shown that relatively high concentrations of ricinoleic acid can cause ultrastructural alterations in the villous tips of the intestinal mucosa but given the high concentrations of ricinoleic acid used in these experiments, it is, however, not clear whether these morphological effects are relevant for the laxative effect of castor oil. It is important to underline that the intestinal mucosal damage was reversible *in vitro* after 2 hours (Gaginella *et al.,*1977) and *in vivo*, the repair being complete after 6 h (**Morehouse *et al*., 1986**), or even longer, up to 9 h post dosing (**Mascolo *et al*., 1984**).

Conflicting data have been published with regard to the ability of ricinoleic acid to induce procontractile effects on intestinal smooth muscle and to alter intestinal ion transport and water flux. Although some researchers observed an inhibition of water and electrolyte absorption, others found an activation of ion secretory processes by ricinoleid acid. In addition to effects on intestinal ion transport and waterflux, evidence has been provided that ricinoleic acid can directly affect intestinal motility. Results from studies with nitric oxide (NO) synthase inhibitors in rats suggest that NO may play a role in the ''diarrhoea effect'' of castor oil. Recently, EP3 receptors have been identified as targets of ricinoleic acid. This could explain, at least partially the *in vivo* effects of castor oil on the motility of the uterus and the intestine in transgenic models.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Watson and Gordon (1962) investigated the absorption of a dose of castor oil (1 ml) administered by stomach tube in rats. Castor oil used was of medicinal grade having the following fatty acid composition: ricinoleic 90%, linoleic 4.7%, oleic 3.2%, stearic 1.0%, palmitic l% and palmitoleic 0.1%. Approximately 7% of the Ricinoleic acid was absorbed within the first 24 h when is administered in fasted rats via stomach tube, whereas Approximately 24% acid was absorbed when the oil was administered to nonfasted animals. Weanling rats fed a diet containing 20% castor oil for eight weeks were found to have 9.7% ricinoleic acid in their fat pads, whereas the level was only 2% in those animals switched at four weeks from the castor oil diet to an olive oil diet for an additional two weeks.

In a study conducted by **Hagenfeldt *et al.*** (1986), castor oil was administered intragastrically to germ-free and conventional rats. Urine was collected at intervals over a 24-h period. The following epoxydicarboxylic acids were detected in the urine of both germ-free and conventional rats: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid. These acids were not detected in urine collected from the rats prior to dosing with castor oil, and they also were not detected in steam-sterilized castor oil. The authors claim that results for the germ-free rat indicate that the cyclization of ricinoleic acid to form an epoxy compound occurs endogenously and does not require the presence of intestinal bacteria.

In a study cited by Cosmetic Ingredient Review Expert Panel, (2007), two groups of five male Wistar rats received 10% castor oil in the diet (cholesterol-enriched and cholesterol-free, respectively) for 20 days. In both dietary groups, a very small quantity of ricinoleic acid was present in perirenal adipose tissue, but not in the serum or hepatic tissue. It was also noted that the perirenal fatty acid profiles did not reflect those of the dietary fats, either in the absence or presence of dietary cholesterol. The fecal

recovery of ricinoleic acid was approximately 0.5% of the total ingested. It was concluded that castor oil was readily absorbed and metabolized.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

In a study conducted by **Capasso *et al.*** (1994), castor oil (2 ml) was administered orally to ten male Wistar rats. The animals were killed and two segments from standardized regions of the duodenum and jejunum were visibly evaluated for macroscopic damage. Copious diarrhea was reported for all animals on days 3, 5, and 7 post dosing. Macroscopic damage, characterized mainly by vasocongestion, was observed throughout the duodenum and jejunum. The injury observed ranged from mild (at 1 h) to severe (at 5 h), and was less severe at 7 h. Injury was not observed at 0.5 or 9 h after dosing. Castor oil–induced mucosal damage was associated with statistically significant intraluminal release of acid phosphatase.

Severe diarrhea, loss of appetite, colic, and fever were reported within 24 h of oral administration of castor oil (2.5 ml/kg) to ponies (**Cosmetic Ingredient Review Expert Panel CIR, 2007**). At 24 h post dose, the mucosa of the cecum and ventral colon had extensive superficial epithelial erosion and neutrophil infiltration. In the ileum, the epithelium of the villous tips was separated from the lamina propria and scanning electron microscopy of the cecal mucosa revealed exposed basement membranes. Ultrastructurally, there was a loss of microvilli, distortion of the cytoplasmic terminal web and other changes. Initiation of regeneration of the intestinal mucosa was evident by 24 h after dosing; at 48 h, denuded basement membranes were covered by cuboidal epithelium and; regeneration was complete by 72 h.

3.3.2. Repeat dose toxicity

Castor oil (Ph.Eur.):

No information available

Castor oil (USP):

In a 13-week study, on F344/N rats and B6C3F1 mice of both sexes exposure to castor oil at dietary concentrations of 0.62%, 1.25%, 2.5%, 5.0% or 10% castor oil, did not affect survival or body weight gains of rats or mice. Mild increases in total bile acids and in serum alkaline phosphatase were noted at various times during the studies in rats receiving the higher dietary concentrations of castor oil. Liver weights were increased in male rats receiving the 10% dietary concentration and in male and female mice receiving diets containing 5% or 10% castor oil. However, there were no histopathologic lesions associated with these liver changes, nor were there any compound related morphologic changes in any organ in rats or mice. According to the authors, because castor oil is composed of triacylglycerols, the increased liver weights could be a reflection of elevated metabolic activity associated with increased lipid absorption, rather than a toxic response (**NTP, 1992**).

3.3.3. Genotoxicity

Castor oil (Ph.Eur.):

No information available

Castor oil (USP):

In a study cited by NTP, castor oil (100-10,000 µg/plate) was not mutagenic in *S. typhimurium* strains TA100, TA1535, TA97, or TA98 when tested with a preincubation protocol in the presence and the absence of exogenous metabolic activation (**NTP, 1992**). Castor oil did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells treated with concentrations up to 5000 µg/ml with and without S9.

No induction of micronuclei was observed in peripheral blood erythrocytes of B6C3F1 mice sampled at the termination of the NTP 13-week study (see repeat-dose studies).

Because the USP monograph does not include specifications for the fatty acid compositions, it is unclear if the result of this study can be extrapolated to oils that comply with European Pharmacopoeia monograph.

3.3.4. Carcinogenicity

Castor oil (Ph.Eur.):

No information available

Castor oil (USP):

Both NTP, on its website (http://ntp-server.niehs.nih.gov; accessed on June 2014) and British Industrial Biological Research Association (BIBRA), in its toxicity profile for castor oil, refer to a long-term toxicology and/or carcinogenesis study having been conducted by NTP (TR-290) with castor oil in the early 1980s. Both indicate that the study was determined to be ''inadequate'' and that a report was never issued.

No other data was found.

3.3.5. Reproductive and developmental toxicity

Castor oil (Ph.Eur.):

No information available

Castor oil (USP):

The repeat-dose study (13-week) conducted by NTP (1992) also investigated the reproductive toxicity of castor oil in rats and mice. A slight decrease in epididymal weight (6% to 7%) was observed in mid- and high-dose groups of male rats; however, this finding was not dose related. No effects on any other male reproductive end point (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive endpoint (estrous cycle length, or time spent in each phase of the cycle) were noted (**NTP, 1992**)

Castor oil (quality unknown):

Gao *et al.* (1998) investigated the effect of castor oil (2 ml/daily) administered by gavage on days 18, 19 and 20 of gestation on the initiation of labour of pregnant rat. The castor oil induced the initiation of labour and shorter the course of the delivery in pregnant rats. Ricinoleic acid was the active component of castor oil-diet in this study.

Later, the same researchers (**Gao *et al.,*** 1999) evaluated in a similar study the effect of castor oil (2 ml/daily) administered by gavage on days 18, 19 and 20 of gestation on the synthesis of prostaglandin

E2 (PGE2) and the induction of labor in pregnant Wistar rats. Compared to the control group, a significant increase in concentrations of PGE2 in tissues of the intestinal mucosa, placenta, amnion, and amniotic cells was noted in test animals.

3.3.6. Local tolerance

In the *Final Report on the Safety Assessment of Ricinus Communis (Castor) Seed Oil* (**Cosmetic Ingredient Review Expert Panel CIR,** 2007) significant data regarding local tolerance of castor oil on different species are included. For example the instillation of undiluted castor oil (0.5 ml) into the rabbit eye resulted in a slight congestion of the iris and conjunctiva in the rabbit eye, but the instillation of castor oil (10 drops daily for 3 weeks) into the eyes of ten rabbits did not produced damage to the corneal epithelium or endothelium. Undiluted castor oil that was applied for 24 h to two areas on the dorsal surface of six albino angora rabbits produced severe skin irritation, while applied to the dorsal skin of male Hartley guinea pigs, male Wistar rats, and miniature swine produced mild skin irritation in guinea pigs and rats, but not in miniature swine.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

The majority of the available toxicological data were obtained with USP grade castor oil). Because the USP monograph does not include specifications for the fatty acid compositions, it is unclear if the toxicological data can be extrapolated to oils that comply with European Pharmacopoeia monograph.)

Single dose toxicity tests with castor oil induced severe diarrhea with mucosal histological damage (loss of microvilli). The effect was reversible after 72 h.

The oral administration of castor oil in a 13-week study, on F344/N rats and B6C3F1 mice at dietary concentrations up to 10% castor oil, did not induced any toxic effect.

Castor oil in AMES assay test with *S. typhimurium* strains TA 1535, TA 98, TA 97, and TA 100 showed a negative outcome. Castor oil did not induce sister-chromatid exchanges or chromosome aberrations in Chinese hamster ovary cells treated with concentrations up to 5000 µg/ml with and without metabolic activation. The micronucleus test on the peripheral blood erythrocytes of mice was also negative. Because the fatty acid composition of castor oil tested is unknown, of these studies cannot be used support the safety of oils complying with the Ph Eur.

Reproductive toxicity data revealed no toxic effect, while developmental studies in pregnant rats suggested that castor oil may have an influence on the initiation of labour. These data are correlated with the recently identification of EP3 receptor as the *in vivo* mediator of the castor oil effects on the motility of the uterus and the intestine (Tunaru *et al.*, 2012)

No carcinogenicity data were available.

3.4. Overall conclusions on non-clinical data

Results from the *in vitro* and *in vivo* studies support the proposed indication. Studies were performed with castor oil and with ricinoleic acid, the active metabolite of castor oil. Non-clinical data revealed that ricinoleic acid has irritant effect on the small intestine through different mechanisms of action, like

alterations in the villous tips of the intestinal mucosa and inhibiting water and electrolytes absorption, or directly affecting the intestinal motility by activating EP3 receptors.

Limited data on pharmacokinetics are available on castor oil after oral administration. Some metabolites (as 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid) were identified in the urine.

Almost all toxicological data were obtained USP castor oil. The specifications of this different from Ph. Eur grade oil. Acute toxicity revealed, as the main outcome, severe diarrhoea accompanied by histological changes on the microvilli, while repeat-dose studies showed no toxic effects. Castor oil (USP grade) was not mutagenic in *S. typhimurium* strains (TA100, TA1535, TA97, or TA98) with or without metabolic, did not induce sister-chromatid exchanges or chromosome aberrations in Chinese hamster ovary cells treated with concentrations up to 5000 µg/ml with and without S9. The micronucleus test in the peripheral blood erythrocytes of mice was also negative. However, because these data were obtained with USP-grade castor oil they can not be used to demonstrate the safety of Ph Eur grade castor oil. Therefore, applications for marketing authorisation of products containing *castor oil(Ph.Eur)* should include data obtained from an AMES test according to the currently valid OECD guideline 471.

Tests on carcinogenicity have not been performed, while developmental toxicity revealed that castor oil could induce the initiation of labour and shorter the course of the delivery in pregnant rats.

Based on information on developmental toxicity, the use during pregnancy and lactation cannot be recommended.

During the longstanding use as a medicinal product in the European Union no serious side effects have been reported. Therefore, the oral administration of castor oil can be regarded as safe under conditions of use that are described in the monograph.

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Ricinoleic acid

The effects of oleic and ricinoleic acids on jejunal absorption have been studied in six healthy volunteers using steady-state jejunal perfusions. Perfusates (at 37^0C) were delivered at a constant rate of 10 ml/min for 90 minutes. Both fatty acids inhibited the electrolyte and water absorption. The changes in water absorption were dose-dependent and, at lower concentrations, there were differences between the potencies of the two fatty acids. Oleic acid inhibited net water movement only when infused at a concentration of 5 mM ($P < 0.01$); it had no effect at lower concentrations. Ricinoleic acid inhibited net water absorption significantly ($P < 0.01$) at a concentration of 0.5 mM in the infusate. At 2 and 5 mM, ricinoleic acid induced net secretion. Ricinoleic acid was the more potent, than oleic acid at 0.5, 2 and 5 mM concentrations ($P < 0.01$), producing fluid secretion when perfused at concentrations at which oleic acid was without effect. Addition of lecithin and monoolein did not diminish the effect of ricinoleic acid; addition of a secretory bile acid (taurodeoxycholate) did not enhance the effect. Authors concluded that the symptomatic consequences of secretion induced by fatty acids are increased water secretion and diarrhea (**Ammon *et al.,*** 1974)

Bretagne *et al.* (1981) tested two conjugated bile salts (10 mmol/l sodium glycocholate and 10 mmol/l sodium taurodeoxycholate) and three laxatives (30 mmol/l magnesium sulphate, 10 mmol/l ricinoleic acid, 2 mmol/l dioctyl sodium sulphosuccinate DOSS) on seven subjects with no intestinal lesions in 14 experiments by intestinal perfusion of the jejunum. A 25 cm segment was studied. Each solution was perfused at the rate of 10 ml/min. Water and electrolyte fluxes, losses of deoxyribonucleic acid (DNA), and intestinal cell enzyme activity were measured in the fluids collected. All the laxatives and bile salts tested (except sodium glycocholate) induced water and electrolyte secretion, a rise in intraluminal DNA loss, and enzyme activity. It was possible to establish a significant correlation ($P < 0.001$) between the amounts of water fluxes and DNA loss under the effect of dioctyl sodium sulphosuccinate and ricinoleic acid. The results confirm the secretory effect on the human jejunum of $MgSO_4$, DOSS and ricinoleic acid.

Table 1 *Water secretion during basal period and under effect of laxatives and taurodeoxycholate (mean ± SEM)*

	Glycocholate (n=3)	*Taurodeoxycholate (n=3)*	*$MgSO_4$ (n=4)*	*DOSS (n=3)*	*Ricinoleic acid (n=3)*
Basal period (ml/min/25 cm)	−0·9±0·3	+0·3±0·3	−0·1±0·2	−0·1±0·2	−0·9±0·3
Laxative perfusion (ml/min/25 cm)	−0·2±0·4	+4·2±0·5	+0·8±0·1	+5·1±0·7	+6·2±2·2

The values indicated under perfusion of laxatives are average values obtained during the first 90 minutes for collection.

Table 2 *Increase in DNA losses and number of cells desquamated during laxative and taurodeoxycholate perfusions (mean ± SEM)*

	Glycocholate (n=3)	*Taurodeoxycholate (n=3)*	*$MgSO_4$ (n=4)*	*DOSS (n=3)*	*Ricinoleic acid (n=3)*
Δ DNA (μg/min/25 cm)	8·3±3·6	55·9±15·3	29·1±11·1	824±92	628±167
Δ Number of intestinal cells × 10^9 desquamed/90 min/25 cm	0·05±0·02	0·50±0·27	0·26±0,09	7·4±0·8	5·6±1·5

Δ DNA is the average value obtained during the first 90 minutes of collection.

Sogni *et al.* (1992) comparared the effects of ricinoleic acid and senna on orocecal and oroanal transit time in 12 healthy subjects, using salacylazosulfapyridine method. The 12 healthy volunteers were: a) under resting conditions; b) 2 weeks later with ricinoleic acid 40 ml (n = 6) or senna 19 mg (X-Prep = 1.2 g; n=6) administration. In each step, Salazopyrin (2 g) and 20 radiopaque markers were ingested with a 200 kcal meal (Polydiet TCM = 200 ml). The following parameters were determined: a) plasmatic level of sulphapyridine (spectrophotometry) at 30 min intervals during 12 h; b) 2-day stool frequency and weight; c) oro-anal transit time (passage of the first marker and half of the markers in stools). In one subject, no sulphapyridine level was detected after administration of ricinoleic acid. With senna, 2 day stool frequency and weight increased by 80 and 131 % respectively: orocecal transit time decreased from 6.1 ± 1.3 to 4.8 ± 1.2 h ($P < 0.01$) and oro-anal transit time (first marker) decreased from 31.8 ± 9.6 to 20.7 ±8.9 ($P < 0.05$). With ricinoleic acid, 2 day stool frequency and weight increased by 212 and 350 %, respectively; orocecal transit time decreased from 5.8 ± 1.8 to 2.2 ± 0.7 h ($P < 0.01$) and oro-anal transit time decreased from 25.3 ± 7.1 to 8.0 ± 6.8 h ($P < 0.05$).

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Castor oil

Watson *et al.* (1963) studied the absorption and excretion of castor oil labeled with ^{131}I in five hypertensive subjects (ages and weights not stated). The composition of the castor oil was as follows: palmitic acid (1%), palmitoleic acid (0.1%), stearic acid (1%), oleic acid (3.2%), linoleic acid (4.7%),

and ricinoleic acid (90%). The doses administered ranged from 4 to 60 g (approximately 6µCi of radioactivity per dose). Small doses of oil were also administered to the three normal volunteers, and free diet was allowed. Stool collections were made during the first 24 h after dosing and during the subsequent 72 h. Urine was collected in 24-h samples. Fecal recovery of ^{131} I(%) ranged from 11.4% (for 10 g dose of castor oil) to 86.0% (for 44.4 g dose of castor oil). The authors concluded that absorption is inversely related to the administered dose, and, that at small doses (4 g), the absorption is virtually complete.

The ingested castor oil is hydrolyzed in the small intestine in humans by pancreatic enzymes, leading to the release of glycerol and ricinoleic acid which, like other anionic surfactants, reduces net absorption of fluid and electrolytes, and stimulates intestinal peristalsis (**Brunton et al., 1990**). Ricinoleic acid is metabolized systemically and the metabolites are excreted.

Hagenfeldt *et al.* (1986) found three epoxydicarboxylic acids in the urine of an anorexic woman after the ingestion of castor oil: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6 epoxydodecanedioic acid. These three metabolites were also detected in the urine of rats.

Ricinoleic acid

The absorption on jejunal mucosa of oleic and ricinoleic acids have been studied in six healthy volunteers using steady-state jejunal perfusions. Studies showed that oleic acid was absorbed twice as fast as ricinoleic acid. Ricinoleic acid was absorbed more slowly from all perfusates and thereby achieved higher mean segment concentrations, despite the greater potential of this fatty acid to produce fluid secretion (**Ammon *et al.*,1974**).

TABLE III
Infusion Concentration, Mean Segment Concentration and Absorption of Fatty Acids in Human Jejunum*

Infusion concn	Oleic acid		Ricinoleic acid	
	Absorption	Mean concn	Absorption	Mean concn
mM	*µmol/min/25 cm*	*mM*	*µmol/min/25 cm*	*mM*
0.5	3.3±0.3	0.31±0.02	2.5±0.7	0.38±0.03
2.0‡	16.2±1.4	0.92±0.16	7.6±2.1	1.55±0.17
5.0§	28.2±4.1	3.18±0.30	10.2±2.4	4.18±0.22
10.0‖	41.9±7.3	6.83±0.43	21.6±2.6	8.02±0.08

Each value is mean (±SEM) from studies in random sequence in four subjects.
* Mean segment concentration, expressed as logarithmic mean of input and recovery concentrations.
‡ $P < 0.005$, absorption of oleic vs. ricinoleic acid.
§ $P < 0.025$, absorption of oleic vs. ricinoleic acid.
‖ $P < 0.05$, absorption of oleic vs. ricinoleic acid.

4.2. Clinical efficacy

4.2.1. Dose response studies

Ricinoleic acid- see 4.1.1.

Castor oil

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Laxative effect

Two clinical trials (one double blind positive controlled and one observational) that investigated the laxative effect of castor oil in constipated patients were found in literature. Both studies are also cited by **Buechi** (2000).

The double blind positive controlled trial was conducted on 60 constipated patients were randomly allocated to took either refined castor oil capsules(corresponding to 1.2 g, 2.4 g or 3.6 g, daily; n=30) or two senna capsules (300 mg extract equivalent to 50 mg of total sennosides; n=30) each for 1 week. The initial dose administered corresponds to 1.2 g refined castor oil but could be increased up to 3.6 g, according to response. The main outcome was to obtain 5 stools/week. This frequency was obtained after 1 week in 15 patients (50%) at dose of 1.2 g/day castor oil, while 2.4 g castor oil produced this frequency in 13 patients (43.3%), and only 2 patients needed the maximum dosage (3.6 g/day). The authors concluded that 4 capsules of castor oil (2.4 g) induced the same effect as 300 mg senna extract capsules (Pawlik, 2000).

The observational study was conducted on 168 constipated patients that took castor oil capsules (each containing 1 g oil) for 14 days. The dosage varied from 1 to 12 capsules/day, the mean dose corresponding to 2.5 g castor oil. The main outcomes were: the stools frequency, the stools consistence, duration of effect, incapacity to work. The assessment was done between Day 4-7 and Day 11-14. An increased on stools frequency was observed after 4-7 days in 81% of the patients and in 87% after the 14 days. The authors concluded that even small doses(2-3 capsules) have an laxative effect, and recommended an average dose on 3-5 capsules (Boneke 1995).

Assessors comments: The described positive effects are in line with the approved well-established use indication (laxative for short term-use) of authorized castor oil medicinal products in EU (since 1976)

Bowel cleaning effect

Slanger *et al.* (1979) conducted a comparative study of a standardized senna liquid preparation and castor oil in preparing patients for radiographic examination of the colon. The study included 100 patients scheduled for barium enema, 44 men and 56 women, 19 to 86 years old, the average age being 60 years. The patients were randomly divided into four treatment groups, which, on subsequent analysis, were found to be approximately matched in sex and age. 25 patients received single full doses of senna liquid preparation (SLP) (2 1/2 oz.) and 25 were given single full doses of castor oil (2 oz.= meaning 56,7 grams), while 26 patients received the divided dose of senna preparation and 24 patients were treated with the two half-doses of castor oil. The safety and efficacy of each method of bowel evacuation was assessed by interview and by radiologic results.

The primary outcome was quality of radiographic visualization which was rated as excellent, good, fair, or poor. The quantities of fecal residue and of gas present at the time of the barium enema, reflected in these ratings, were individually evaluated and graded by means of a numerical scale ranging from 0 through 3 + (0 = none, 1+ = small, 2 + = moderate, and 3 + = large quantity). The verbal inquiries concerned side effects most commonly associated with purgation; specifically, nausea, griping, cramping, and abdominal pain. Senna preparation was highly superior to the single-dose technique involving castor oil, and more effective than the divided-dose method of administering this agent. Visualization was excellent in 96% of cases in either series of patients treated with senna preparation, but only in 24 % and 50 %, respectively, of the groups given the single or divided dose of castor oil. The group treated with the single dose of castor oil showed substantially more residue than either set

of patients given SLP; the divided dose of castor oil was more effective in the removal of this material, but less than SLP, however administered.

The side effects induced by the single castor oil were: nausea (2 patients/25 total patients), griping(11/25), cramps(12/25) and abdominal pain(11/25). For the divided dose the incidence was almost similar, but the severity was lower.

Novetsky *et al.* (1981) tested different modes of colon cleansing regimes prior to gallium-67 scintigrams to investigate colonic accumulation of gallium-67, which frequently complicates the interpretation of the scintigrams. 309 patients were randomly assigned to one of 4 cleansing regimes: (1) 78 patients undertook a high fibre diet (minimum of 11.2 g fiber and 6 to 8 cups of fluid each day 3 consecutive days prior to scintigram); (2) 76 patients took 30 ml of castor oil each night for 2 consecutive nights before scintigram; (3) 76 patients took 30 ml of milk of magnesia (no further information is given) and 5 ml of cascara (the amount of anthranoides is not defined) each night for 3 consecutive nights before scintigram; (4) 79 patients did not undertake any preparation. Patient compliance rates for the 4 regimes were 17%, 32%, 36%, and 46%, respectively. Gallium-67 scintigrams were graded for colonic activity on a scale of 0-3 by 3 independent observers. 3 represents a bowel with the highest gallium-67 activity. Gallium-67 activity in the colon was significantly less after administration of castor oil than after no preparation (p=0.047). A high fibre diet also resulted in a substantial reduction in colonic activity when compared with no preparation but without statistical significance (p=0.083). Regimen 3 did not produce significantly better results than regimen 4 (p=0.42). Authors suggested that the differences reported in the efficacy may be due, at least in part, to differences in the compliance rate of the population studied.

Gould *et al.* (1982) compared the effects of castor oil and senna preparation in colonoscopy in patients with inactive chronic ulcerative colitis. A prospective trial was conducted on 46 patients (26-71 years old) that were randomly allocated to bowel preparation with either castor oil (30 ml, orally; n=23; 13 men:10 women); or five double-strength senna tablets (equivalent to 75 mg of total sennosides; n=23; 12 men: 11 women). All patients took the laxative 4 hours before colonoscopy. Colonoscopy was preceded by at least two tap water washout edemata. The adequacy of bowel preparation was recorded by the endoscopist (without knowing which laxative was used) as being perfect, adequate or poor (no other details are provided). Castor oil produced the following outcomes: "perfect" outcome (5/23), acceptable (14/23) and poor (4/23), while senna induced "perfect" outcome (7/23), acceptable (13/23) and poor (3/23). No difference was observed between the two preparations, which gave adequate bowel preparation in 39 of 46 patients (85%).

Present *et al.* (1982) evaluated 12 colon-cleansing regimens with single-contrast barium enema. 1,435 patients were examined at six different institutions with 12 different preparation protocols. For each protocol 25 patients were examined. There were 2,870 films evaluated by seven different radiologists who were blind to both the institution and the preparations used. The protocols used correspond to: Protocol 1 (water enema); Protocol 2 (4 packages of product "CE" [1.5 g 4,4-diacetoxydiphenylpyridyl-2)-methane + 4 x 2.5 tannic acid] in 2 L enema) Protocol 3 (2 ounces of castor oil); Protocol 4 (one bottle of product containing 2.5 ounces of senna extract,(SEP)); Protocol 5 (2 ounces castor oil + 2 L water enema); Protocol 6 (2 ounces* castor oil + 2 L enema containing 4 packages of "CE") Protocol 7 (one bottle SEP, containing 2.5 ounces of senna extract+ 2L water enema); Protocol 8 (one bottle SEP +2 L enema containing 4 packages of "CE") Protocol 9 (bisacodyl 20 mg, orally+ 2 L water enema); Protocol 10 (bisacodyl 20 mg, orally+ 2 L enema containing 4 packages of "CE"); Protocol 11 (bisacodyl 20 mg orally + bisacodyl 10 mg suppositories); Protocol 12 (a bottle of magnesium citrate +3 x 20 mg bisacodyl, orally + 10 mg bisacodyl suppositories). The radiologists judged the acceptability of the final results on the basis of the presence or absence of

particulate matter in each part of the colon (1 = no particulate matter; 2 = particulate matter between 0 and 5 mm in diameter; 3 = particulate matter greater than 5 mm but less than 1 cm in diameter; 4 = particulate matter more than 1 cm in diameter; 5 = Grossly inadequate preparation (e.g., excessive foreign matter, gas, fluid).

Protocols 9, 5, 7, and 12, in this order, are best overall, pre-evacuation, post-evacuation and for conclusions as well as for all parts of the colon (with an insignificant exception for rectum plus rectosigmoid). The superiority of protocols 9, 5, and 7 over the other protocols is highly significant ($p < 10^{-5}$). The authors concluded that bisacodyl 20 mg, orally **+** 2 L tap water enema is better than all the other protocols in all parts of the colon for both genders and all ages. Bisacodyl or castor oil or SEP, each with 2 L water enema, are logically similar and better than the other protocols. Water enema only or castor oil only is the least effective protocols.

* 2 ounces = 56,7 grams

The side effects induced by the Protocol 5 (56,7 g castor oil + 2 L water enema) were: nausea (29%), interference with sleep (31%), severe cramp (35%), faintness (16%), bleeding (8%).

Strates and Hofmann (1987) investigated in a randomized study carried out in 195 out-patients (with age between 19-81 years old) the efficacy of a commercially-available bowel evacuant kit (magnesium citrate oral solution, phenolphthalein tablets and a bisacodyl suppository) and castor oil with enemas. The doses administered corresponded to 2 oz. (meaning 56 g) castor oil (orally, as single dose) followed by tap water enemas or one commercially evacuant kit (containing 10 oz. magnesium citrate oral solution+ 2 phenolphthalein tablets (each of 130 mg) + 10 mg bisacodyl suppository). About 80% of the patients had regular bowel habits, 20% had a history of diarrhoea and 23% constipation. The adequacy of the bowel evacuation procedure was based on evaluation of flat plate and post-radium enema X-rays by a radiologist. Evaluation criteria included quantitation of amounts of faecal material, presence and location of gas and fluid, overall evaluation of the colon preparation and evaluation of post-evacuation films. The amounts of faecal matter, gas and fluid remaining in the colon subsequent to bowel evacuation were not statistically different in the two groups of patients. Overall evaluation of large bowel preparation was satisfactory in more than 98% of patients while bowel cleanliness, as determined by the ability to detect a 1 cm lesion, was adequate in 95% of patients using either preparation. Patient acceptance was in favour of the commercial preparation in that fewer patients using it found the procedure uncomfortable or indicated a preference for another evacuant than did those prepared with castor oil and enemas.

Yang HZ *et al*. *(*1990) compared the effectiveness of six cleansing methods used in colonoscopy: (1) normal saline enema, (2) castor oil with normal saline enema, (3) castor oil with soapsuds enema, (4) magnesium citrate with normal saline, (5) magnesium citrate with soapsuds enema and (6) ingestion of Golyetly solution. The total number of patients was 247, age distribution was 43 +/- 15 years old, and sex distribution was 133 males and 114 females. The authors have compared and determined the degree of cleanliness by an experienced endoscopist. The grade I and II represented no difficulties at performing the fiber optic colonoscopy+, but grade III and IV had some difficulties, even unable to perform the fiber optic colonoscopy. The effectiveness the cleansing agents, represented with grade I and II was 95.9% (47/49) in method 6, 93.2% (54/58) in method 2, 83.3% (30/33) in method 3, 70.0% (28/40) in method 5, 66.7% (16/24) in method 1, and 45.7% (18/40) in method 4. Method 2 and 6 were the most effective in normal bowel habit patients. In constipated patients, method 6 was the most effective and all method except method 4 were effective in diarrhoea patients. The degrees of less mucosal irritation by various bowel cleansing method were in the order of method 6(100%),

1(100%), 5(74%), 2(69%). In subjective symptoms and cleansing groups, abdominal distension, pain, nausea and vomiting were complained, and that's subject symptoms were in the order of method 3(88.9%), 6(79.6%), 1(75%), 5(72.5%), 2(72.4%), 4(67.5%).

Mundinger A *et al*. (1990) investigated in a controlled study the efficiency of cleansing out the colon and the best contrast medium of two different regimens (total n = 237) for preparing the colon for double-contrast examination. The recommendations regarding diet and liquid intake, contrast medium and examination technique were identical in both groups. The combination laxative "X" (5 mg bisacodyl and 7.217 g sodium phosphate; n=118) without cleansing enema resulted in a more thoroughly cleaned colon that castor oil capsules (n=119, 30 capsules/day, each contains 1 g castor oil, g orally) with cleansing enema (very good/good cleanliness: "X" combination, 92.4%; castor oil, 83.2%, $p < 0.05$). However, the quality of contrast medium (good: "X" combination 71.2% as opposed to castor oil 74.8%) was (independent of the preparation method) below standard regarding cleansing of the colon.

Kolts *et al.* (1993) compared the effectiveness and patient tolerance of oral sodium phosphate, castor oil, and standard electrolyte lavage for colonoscopy or sigmoidoscopy preparation. 113 patients were randomized to receive either 90 ml sodium phosphate oral (n=34), lemon-flavored castor oil 60 ml (that contains 95% castor oil), orally (n=41), or 4 L standard polyethylene glycol-based lavage solution (n=38) before elective colonoscopy. From the included patients just 8 were constipated (5 were treated with polyethylene glycol-based lavage solution and 3 with sodium phosphate). The quality grades used for the colon cleansing were: excellent (small volume of liquid easily aspirated, but covering less than 5% of the colonic surface), good (volume of clear liquid covering 5-25% of the surface but could be easily aspirated to expose nearly all the mucosa), fair (stool limited the examination but 90% or more of the mucosa could be examined) and poor(less than 90% of the mucosa could be examined) Scores for cleansing the entire colon as determined by endoscopists who were blinded to the cathartic agent were highest in patients receiving sodium phosphate ($p < 0.02$). Scores of left-colon cleansing for flexible sigmoidoscopy were equally high for the three methods. Scores for taste and symptom side effects were similar for each preparation. The authors concluded that oral sodium phosphate is a cost-effective colonoscopy preparation that is better tolerated and more effective than the polyethylene glycol-electrolyte lavage solution or castor oil.

Chen *et al.* (1999) compared colon cleansing efficacy, patient acceptance and side effects in patients given either a magnesium citrate-bisacodyl or a castor oil regimen prior to colonoscopy. Seventy outpatients scheduled for colonoscopy were randomized to receive one of two bowel evacuation regimens on the day prior to the examination. Group 1 (n = 36) received a magnesium citrate solution (250 mL) and bisacodyl (10 mg, orally). Group 2 (n = 34) received castor oil (60 mL, orally). Bowel cleanliness was scored as: 3 (no faecal materials in the colon); 2 (faecal materials present in the colon but not enough to interfere with de endoscopist's diagnosis) and 1 (faecal materials present in the colon and interfering with diagnosis). The sum of from the two observers were ranked from 6 to 2. The cleansing effect of the magnesium citrate-bisacodyl regimen, assessed by the cleanliness score was significantly better than that of castor oil in the ascending colon and caecum (cleansing scores 5.2+/-1.2 vs 3.5+/-1.3, $P< 0.0001$), but similar to that of castor oil in the recto-sigmoid, descending and transverse colon.

Comparative cleanliness scores magnesium citrate+ bisacodyl vs. castor oil

	Magnesium citrate + bisacodyl	Castor oil	p
Rector-sigmoid colon	5.2 ± 1.1(35)	5.2 ± 1.4(34)	NS
Descending colon	5.5 ± 1.0(33)	5.3 ± 1.3(33)	NS
Transverse colon	5.3 ± 1.1(32)	5.1 ± 1.3(32)	NS
Ascending colon/caecum	5.2 ± 1.2(27)	3.5 ± 1.3(24)	< 0.0001

Results are mean ± SD. Figures in parentheses are the number of the patients. NS: not significant

Regarding the side effects observed, abdominal pain (38 vs. 11, P< 0.01) and nausea (29 vs. 8, P<0.05) were significantly more common in patients receiving the castor oil preparation than in patients administered with the magnesium citrate-bisacodyl regimen. More patients complained of poor acceptance with the castor oil regimen than with the magnesium citrate-bisacodyl regimen (24 vs. 8%, P=0.06).

Side effects of magnesium citrate+ bisacodyl and castor oil regimens for colonoscopy

Side effects	Magnesium citrate + bisacodyl	Castor oil
Nausea (%)	3(8)	10(29)
Vomiting (%)	2(6)	6(18)
Abdominal pain (%)	4(11)	13(38)
Abdominal fullness (%)	4(11)	6(18)
Fainting	4(19)	8(24)

Figures in parentheses are the percentage

Hsieh *et al.* (2000) used two different cathartics to evaluate the efficacy of bowel cleansing in improving the quality of abdominal gallium imaging. One hundred and fifty patients underwent gallium scintigraphy and were randomly divided into three groups. Group A received no bowel preparation, Group B received 30 ml of castor oil the night before imaging, and Group C received bisacodyl 10 mg the night before imaging. Gallium activity in the intestine was rated on a three-point scale from 0 to II based on the anterior view of a delayed 48-h gallium image. The data showed that the incidence of gallium accumulation in the small intestine was low. On the contrary, there was high prevalence of gallium activity in the colon. 48% of Group A patients had obvious gallium activity in the colon. The percentage decreased significantly to 28% and 22% in Groups B and C, respectively. No significant difference was noted between Group B and Group C. The data suggest that the application of either castor oil or bisacodyl significantly improves the quality of 48-h abdominal gallium scintigraphy. There were no significant differences in the efficacy of bowel cleansing on gallium activity between these two laxatives.

Yang *et al.* (2005) compared the efficacy of castor oil and bisacodyl, in the routine bowel preparation of outpatients for intravenous urography (IVU). They used castor oil in patients undergoing IVU for 1 month, and then used bisacodyl in patients undergoing IVU for another month. Two uroradiologists, unaware of the method of bowel preparation, reviewed the standard radiographs and graded the residue in the large bowel and the clearness of the opacified urinary collecting system. In total, 71 consecutive outpatients received castor oil (80 ml as an emulsion) and 84 received bisacodyl (15 mg),

on the evening before IVU. To evaluate the degree of faecal residue on plain abdominal images, the following grading system was created: if there was residue in more than two-thirds of a specific film area the score was 0 ; if residue was seen in less than two thirds, but more than one-third, of a specific film area, the score was 1; if residue was seen in less than one-third of a specific area of the film, the score was 2; and if no residual fecal material was seen, the score was 3. When the laxative effect of the two agents was compared, no difference was found in the grading of fecal residue on plain abdominal images ($p = 0.14$), or in visualization of the urinary system on the left ($p = 0.31$) and right sides ($p = 0.98$). In conclusion, authors did not observed difference in laxative efficacy between castor oil and bisacodyl.

Apisarnthanarak *et al.* (2009) compared efficacy for colon cleanness and side effects of castor oil and sodium phosphate preparation. 100 patients included in the study were 39 males, 61 females with age range between 22-82 years (mean = 53.0, SD = 13.5). The patients referred for barium enema were randomized to receive castor oil 30 ml, orally (n = 50) or 90 ml of sodium phosphate preparation (n = 50). The efficacy for colon cleanness was graded by two radiologists using a 5-point scale [1 = excellent (colon is totally clean), 2 = easy for evaluation (few remaining stools, interpretation is easy), 3 = acceptable (some remaining stools, interpretation could be done reasonably), 4 = difficult for evaluation (lots of stool, barium enema could be evaluated with difficulty), and 5 = unacceptable (full of stools, study could not be evaluated)]. Side effects were evaluated by patients' vital signs, total number of bowel frequency, and 10 associated symptoms. Among 100 recruited patients, four (two in each group) were excluded from the evaluation of colon cleanness due to incomplete barium enema. The average cleanness scores were very similar for the sodium phosphate and castor oil groups (mean $\pm$ SD: 2.78 $\pm$ 0.54 vs. 2.75 $\pm$ 0.54, median: 3.0 vs. 3.0) with non significant statistical difference ($p = 0.130$). If the average cleanness score of less than or equal to 3 were considered as adequate, sodium phosphate resulted in adequate colon cleanness for 87.5% (42/48) compared to 93.8% (45/48) in castor oil ($p = 0.486$, 95% CI of difference (sodium phosphate-castor oil) = -19.5%, 6.2%). The total number of bowel frequency was higher in the sodium phosphate group than castor oil group. The means (+ SD) of total number of bowel frequency in each group were 11.1 + 5.1 and 5.8 + 3.0, respectively ($p < 0.001$).

Regarding side effects (dizziness, nausea, vomiting, abdominal cramping, rectal pain, incontinence, thirsty, palpitation, fatigue, and fainting), only the nausea symptom score tended to be higher in the sodium phosphate group ($p = 0.067$). The incidence of castor's oil side effects was: dizziness (15%), nausea (44%), vomiting (6%), abdominal cramping (38%), fatigue (32%), fainting (6%), palpitation (6%), incontinence(30%).

Sani *et al.* *(*2010) compared the efficacy, adverse effects and patient compliance of two bowel preparation regimens with castor oil and a syrup containing senna (ScS) in of outpatients for Intravenous Urography (IVU). 114 consecutive outpatients were randomized to receive either the standard bowel preparation with 60 mL of castor oil (n=57) or the test method with 60 mL of ScS (n=57) before IVU examination. Two radiologists scored the bowel cleansing on a 0-3 scale, so the sum of the two scores was in the range of 0 to 6. The compliance and acceptability of both regimens were assessed by using structured questionnaires filled by the patients. The Numbers, ages, weights and gender distribution of patients and their prior bowel preparation experience in the two groups did not differ significantly. The cleanliness scores for the castor oil and ScS group were 3.97 ± 0.971 and 4.87 ± 0.917, respectively, indicating that ScS p causes a better bowel cleansing compared castor oil. Most of the patients in ScS group had completed the bowel preparation process, whereas 11 patients in castor oil group (19.3%) could not swallow the castor oil completely.

The incidence and severity of some of the adverse effects was significantly higher in castor oil group: nausea (56.1%), vomiting (54.4%), abdominal pain (63.2%), thirst (56.1%), abdominal fullness (68.4%) and insomnia (50.8%). However, the incidence and severit of anal irritation was higher in ScS group. Although the incidence of diarrhoe was higher in ScS (100% vs. 91.2% for castor oil) but its severity was higher in castor oil group.

Dadkhah *et al.* (2012) assessed whether bowel preparation prior to kidney-ureter-bladder (KUB) radiography and intravenous urography (IVU) are of value in improving visualization of the urinary system. A total of 186 patients participated in this study. Thirty-nine patients with chronic constipation based on Rome III criteria* and 147 patients with normal bowel habits were included. All the patients were randomly divided into two groups. Patients in group 1(n=17 constipated and n=74 normal) received castor oil (80 ml) before imaging and had to eat or drink nothing after midnight. Patients in group 2(n=22 constipated and n=73 normal) were allowed to eat and drink before the examination and received no bowel preparation. Kidney-ureter-bladder radiographies were obtained in all the patients and IVUs were indicated in 77 patients. To assess the image quality, radiographic images were divided into 5 anatomical regions and each region was scored from 0 to 3 based on obscurity of the images by the bowel gas or fecal residue. Mean total score for visualization of the urinary system on plain and contrast images did not differ significantly between the two groups (P =0.253). However, patients with chronic constipation who received castor oil revealed a significantly better visualization score on plain images (P =0.001). Of 91 patients who has received castor oil, moderate or severe abdominal pain occurred in 21(23.1%), nausea in 9 (9.9%) and vomiting in 4 (4.4%) patients. Thirty-seven (40.6%) patients reported the effects of castor oil as unpleasant and 15 (16.5%) as very unpleasant.

Table 6: Clinical studies on humans
RCT= randomised control trial; RPT= randomised positive control trial ; IVU= intravenous urography

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score**	**Comments on clinical relevance of results**
Laxative effect							
Buechi (2000)	double blind RPT	castor oil capsules (1.2 g, 2.4 g or 3.6 g, daily) 300 mg senna extract capsules (equivalent to 50 mg of total sennosides) Duration of treatment: 1 week	60 constipated patients Castor oil(n=30) Senna extract(n=30)	Constipated patients(no criteria included)	Primary outcome: to obtain 5 stools/week This frequency was obtained: in 15 patients (50%) after 1.2 g/day castor oil/day in 13 patients (43.3%) after 2.4 g castor oil/day in 2 patients after 3.6 g castor oil/day	none	4 capsules of castor oil (2.4 g) induced the same effect as 300 mg senna extract capsules.
Buechi (2000)	Observational trial	1 g castor oil capsules The dosage varied from 1 to 12	168 constipated patients	Constipated patients(no criteria included)	Primary outcome: the stools frequency. An increased on stools frequency was observed		Small doses as 2-3 g castor oil had an laxative

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments on clinical relevance of results
		capsules/day, Mean dose =2.5 g castor oil. Duration of treatment: 14 days			after 4-7 days in 81% of the patients and in 87% after the 14 days.		effect

Bowel cleaning effect

Slanger et al.,1979	RPT	Senna liquid prep. Castor oil Single dose of Senna liquid (2 1/2 oz.); Single dose of castor oil (2 oz.=56,7 g); 2 x 1 oz. Senna liquid; 2 x 1 oz. castor oil; Orally Duration: single administration	100 patients (44 male 56 female; 19 -86 years old, (average =60) Single dose of Senna liquid (n=25) Single dose of castor oil (n=25) 2 doses of Senna liquid (n=26)	Preparing for colonoscopy	Primary outcome: quality of radiographic visualization Visualization was excellent in 96% of cases treated with Senna liquid, but only in 24 and 50 %, respectively, of the groups given the single or divided dose of castor oil.	None	Castor oil was less efficient than Senna Liquid

			2 doses of castor oil (n=24) Drop out: none				
Novetsky et al.,1981	RCT	(1) high fiber diet min 11.2 g fiber/ day, 3 days ; (2) 30 ml of castor oil/night, 2 nights (3) 30 ml of milk of magnesia + 5 ml cascara/night, 3 nights; (4) control Duration: 2 or 3 days	394 patients High fiber diet (n=78) Castor oil (n=76) milk of magnesia + cascara control (n=79) Control(n=79) Drop out:85	Cleansing the colon in Galium scintigraphy	Primary outcome: colonic activity(assessed based on gallium activity) Gallium-67 activity was significantly less after regimen 2 than control (p=0.047). Regimen 1 resulted in a substantial reduction in colonic activity compared with control but without statistical significance (p=0.083). Regimen 3 did not produce significantly better results than control (p=0.42).	Student's t-test	Irrelevant results due to the poor compliance rate (32%)
Gould et al., 1982	RPT, double - blind	Castor oil (30 ml) Senna tablets (equivalent to 75 mg of total sennosides). Orally, 4 hours before colonoscopy. Colonoscopy was preceded by at least two tapwater washout edemata. Duration: single administration	46 patients Castor oil n=23 26-71 years old 13 male 10 female Senna tablets n=23 27-67 years old 12 male 11 female	Preparing for colonoscopy in patients with inactive chronic ulcerative colitis	Primary outcome: the adequacy of bowel preparation Castor oil: perfect bowel preparation (5/23), acceptable (14/23), poor(4/23) Senna: perfect bowel preparation (7/23), acceptable (13/23) and poor(3/23).	None	No difference was demonstrated between the two preparations
Present at al., 1982	RCT, multicentric	**1**: water enema **2** : 4 x 1.5 g 4,4-diacetoxydiphenylpyridyl-2)-methane + 4 x 2.5 tannic acid in 2 L enema (CE)	1,800 patients For each protocol 25 patients were examined, at six different	Colon-cleansing regimens with single-contrast barium enema	Primary outcome: presence or absence of particulate matter in each part of the colon.	None	Water enema only or castor oil only are the least effective protocols.

		3: 2 oz. castor oil **4**: 2.5 oz. senna extract **5:** 2 oz. castor oil + 2 L water enema **6:** 2 oz. castor oil + 2 L CE **7:** 2.5 oz senna extract+ 2L water enema **8:** 2.5 oz. senna extract +2 L CE 9 bisacodyl 20 mg, orally+ 2 L water enema **10:** bisacodyl 20 mg (p.o) + 2 L CE **11** : bisacodyl 20 mg (p.o) + bisacodyl 10 mg suppositories **12:** magnesiun citrate +3 x 20 mg bisacodyl, p.o + 10 mg bisacodyl suppositories. Orally and rectal administration Duration: single administration	institutions Drop out: 365				
Strates and Hofmann, 1987	RPT, double - blind	Castor oil 2 oz. followed by tap water enemas Evacuant kit (10 oz. magnesium citrate oral solution+ 2 x 130 mg phenolphthalein tablets + 10 mg bisacodyl suppository) Orally Duration: single administration	195 patients (19-81 years old) 80% with regular bowel habits 20% diarrhoea 23% constipated Evacuant kit bowel (n=91) Castor oil (n=86) Drop out: 20	Prior to bowel radiological examination	Primary outcome: the adequacy of the bowel evacuation procedure *Castor oil* Faecal matter: little(86%); moderate(12.8%); extensive (1.2%) Gas in colon: little (89.5%) moderate(10.5%); Fluid remaining in the colon: little(94.2%); moderate(5.8%); Colon clean enough to detect 1 cm lesion(95.3%)	Student's t-test	The efficacy was similar

					Evacuant kit Faecal matter: little(83.5%); moderate(16.5%) Gas in colon: little (85.7%) moderate(14.3%); Fluid remaining in the colon: little (89%); moderate(11%); Colon clean enough to detect 1 cm lesion(94.5%) Not statistically different in the two groups of patients.		
Yang et al., 1990	RCT	1. normal saline enema, 2. castor oil + normal saline enema, 3. castor oil + soapsuds enema 4. magnesium citrate +normal saline enema 5. magnesium citrate +soapsuds enema 6. PEG solution Orally Duration: single administration	N= 247, age: 43 +/- 15 years old 133 males 114 females Protocol 1 (n=24) Protocol 2(n=58) Protocol 3 (n=33) Protocol 4(n=40) Protocol 5(n=40) Protocol 6 (n=49)	Prior to colonoscopy	Primary outcome: the effectiveness of various cleansing solutions (as grades I to IV) Method 2 and 6 were the most effective in normal bowel habit patients, while in constipated patients, method 6 was the most effective.	None	Castor oil was less effective compared with PEG solution
Mundinger et al., 1990	RPT	The combination laxative (5 mg bisacodyl and 7.217 g sodium phosphate) without cleansing enema Castor oil capsules(30 capsules/day, each with 1 g castor oil) with cleansing enema Orally	237 patients The combination laxative (n=120) Castor oil (n=117)	Preparing the colon for double-contrast examination	Primary outcome: the efficiency of cleansing out the colon Very good/good cleanliness: Prepacol 92.4% Castor oil 83.2% ($p < 0.05$)	Student's t-test	Bisacodyl +sodium phosphate without cleansing enema was more efficient than castor oil with cleansing enema. The quality of contrast medium was below standard requirements in both cases

		Duration: single administration					
Kolts et al.,1993	RPT, double blind	90 ml Sodium phosphate Lemon-flavored Castor oil (60 ml, contains 95% castor oil) 4 L PEG lavage solution Orally Duration: single administration	113 patients Sodium phosphate (n=34) Castor oil (n=41) PEG lavage (n=38) 8 constipated (5 treated with PEG lavage and 3 with sodium phosphate)	Preparing for colonoscopy or sigmoidoscopy	Primary outcome: Scores for cleansing the entire colon Scores for cleansing the entire colon were the highest for sodium phosphate ($p<0.02$). Scores of left-colon cleansing were equally for the three methods.	Student's t-test	Sodium phosphate is better tolerated and more effective than the PEG-electrolyte lavage solution or castor oil.
Chen et al., 1999	RPT	Castor oil (60 mL) Magnesium citrate solution (250 mL) and bisacodyl (10 mg) Orally Duration: single administration	70 patients Castor oil (n = 34) Magnesium citrate + bisacodyl (n = 36)	Preparing for colonoscopy	Primary outcome: Bowel cleanliness score(BCS) In the ascending colon and caecum: BCS castor oil = 3.5 $\pm$1.3 BCS magnesium citrate + bisacodyl = 5.2 $\pm$1.2 ($P<0.0001$) In the recto-sigmoid, descending and transverse colon: BCS were similar (5.2 $\pm$ 1.3 vs 5.3 $\pm$ 1.1)	Student's t-test	Magnesium citrate-bisacodyl regimen was more efficient than castor oil
Hsieh et al.,2000	RCT	Control Castor oil 30 ml Bisacodyl 10 mg Orally, on the night before imaging Duration: single administration	150 patients	Prior to scintigraphy	Primary outcome: the efficacy of bowel cleansing (assessed based on Gallium activity in the intestine 48% of the control group 28% (castor oil) and 22% (bisacodyl) had gallium activity in the colon.	None	No significant differences between the two laxatives.
Yang et al., 2005	RPT	Castor oil emulsion (80 ml) Bisacodyl(15 mg) before IVU	155 patients Castor oil (n=71) bisacodyl	Bowel preparation for IVU	Primary outcome: fecal residue in the large bowel (assessed by score). Fecal residue score:	Student's t-test	No difference in laxative efficacy between castor oil and bisacodyl

		Duration: single administration	(n=84)		Castor oil: 1.387 ±0.817 Bisacodyl 1.529 ±0.767 (P=0.14)		
Apisarnthanarak et al., 2009	RPT	Castor oil 30 ml Sodium phosphate preparation 90 ml Orally Duration: single administration	100 patients 39 males, 61 females 22-82 years old (mean = 53.0). Castor oil (n = 50) Sodium phosphate (n = 50) Drop out: 4 patients	Bowel preparation	Primary outcome: the colon cleanness (assessed using a 5-point scale) The average cleanness scores: Sodium phosphate vs. castor oil (2.78 ± 0.54 vs. 2.75 ± 0.54) (p = 0.130) A cleanness score ≤ 3 was obtained for 87.5% in sodium phosphate group and for 93.8% in castor oil group (p = 0.486). Number of bowel frequency: Sodium phosphate:11.1± 5.1 Castor oil: 5.8 ± 3.0 (p < 0.001)	Student's t-test	No difference in efficacy between castor oil and sodium phosphate
Sani et al., 2010	RPT Duration: single administration	Castor oil(60 ml) Sena-Graph syrup (60 ml)	114 patients Castor oil(n=57) Sena-Graph syrup (n=57) Drop out: 11	Bowel preparation before IVU	Primary outcome: the bowel cleansing The cleanliness scores: Castor oil: 3.97 ± 0.971 Sena-Graph: 4.87 ± 0.917 (p =0.000)	Student's t-test	Sena-Graph syrup was more efficient compared to castor oil
Dadkhah et al., 2012	RCT	Castor oil (80 ml), orally, single dose Control Duration: single administration	186 patients 39 patients with chronic constipation 147 patients with normal bowel habits Castor oil (n=17	Bowel preparation before kidney-ureter-bladder radiographies	Primary outcome: visualisation score Patients with constipation: castor oil (11.53 ± 2.40) control(8.81 ± 2.32) (p=0.001) Patients with normal	Student's t-test	Patients with chronic constipation who received castor oil revealed a significantly better visualization score.

			constipated n=74 normal) Control (n=22 constipated n=73 normal)		bowel habits castor oil (12.04 ± 1.91) control(12.36 ± 1.62) (p=0.253)		

Table 7. Comparative results of bowel cleaning effect of castor oil

(enema vs. without enema)

Study Reference	**Test Products Dosage Regimen**	**Clinical relevance of results**
With enema (4 studies)		
Gould et al., 1982	Castor oil (30 ml) Senna tablets (75 mg of total sennosides) Single administration	No difference between the two preparations
Strates and Hofmann, 1987	Castor oil (2 oz.=56,7 g) Evacuant kit (magnesium citrate + phenolphthalein + bisacodyl) Duration: single administration	The efficacy was similar
Yang et al., 1990	1. normal saline enema, 2. castor oil + normal saline enema, 3. castor oil + soapsuds enema 4. magnesium citrate +normal saline enema 5. magnesium citrate +soapsuds enema 6. PEG Duration: single administration	Castor oil was less effective compared with PEG solution
Mundinger et al., 1990	The combination laxative (5 mg bisacodyl and 7.217 g sodium phosphate) without enema Castor oil capsules(30 g) with enema Single administration	Bisacodyl +sodium phosphate was more efficient than castor oil
Without enema (10 studies)		
Slanger et al.,1979	Senna liquid (2 1/2 oz); Castor oil (2 oz.=56,7 g) Single administration	Castor oil was less efficient than Senna preparation
Novetsky et al.,1981	1. High fiber diet (min 11.2 g/day) 3 days 2. 30 ml of castor oil/night, 2 nights 3. 30 ml of milk of magnesia + 5 ml cascara/night, 3 nights; 4. control	Irrelevant results
Present at al., 1982	1: water enema 2 : 4 packs Clysodrast in 2 L enema (CE) 3: 2 oz. castor oil 4: 2.5 oz. senna extract 5: 2 oz. castor oil + 2 L water enema 6: 2 oz. castor oil + 2 L CE 7: 2.5 oz senna extract+ 2L water enema 8: 2.5 oz. senna extract +2 L CE 9 bisacodyl 20 mg, orally+ 2 L water enema 10: bisacodyl 20 mg (p.o) + 2 L CE 11 : bisacodyl 20 mg (p.o) + bisacodyl 10 mg suppositories 12: magnesiun citrate +60 mg bisacodyl, p.o + 10 mg bisacodyl suppositories. Single administration	Water enema only or castor oil only are the least effective protocols.
Kolts et al.,1993	90 ml Sodium phosphate Lemon-flavored Castor oil (60 ml, contains 95% castor oil) 4 L PEG lavage solution Single administration	Sodium phosphate is more effective than the PEG- lavage or castor oil.
Chen et al., 1999	Castor oil (60 mL) Magnesium citrate solution (250 mL) + bisacodyl (10 mg) Single administration	Magnesium citrate-bisacodyl regimen was more efficient than castor oil
Hsieh et al.,2000	Castor oil 30 ml Bisacodyl 10 mg Single administration	No significant differences between the two preparation
Yang et al., 2005	Castor oil emulsion (80 ml) Bisacodyl(15 mg) Single administration	No significant differences between the two preparation
Apisarnthanarak et al., 2009	Castor oil 30 ml Sodium phosphate prep 90 ml Single administration	No significant differences between the average cleanness scores of the two preparation
Sani et al., 2010	Castor oil(60 ml) Senna syrup (60 ml)	Senna caused a better bowel cleansing compared castor oil

Dadkhah et al., 2012	Castor oil (80 ml) Control Single administration Constipated/normal habits	Patients with chronic constipation that received castor oil revealed a significantly better visualization score

Assessor comments:

Trials treatment with Castor oil were performed with or without a supplement treatment with an enema.

With enema were found 4 studies: in two studies there was no difference between the efficacy of the preparations used (castor oil vs. senna and castor oil vs. mixture of magnesium citrate, phenolphthalein and bisacodyl), while in one study PEG exhibited a better bowel cleaning effect and in another one the combination of bisacodyl and phosphate was more efficient compared with castor oil.

Without enema were found 10 studies. Only one study had irrelevant results (not significantly different from the control, due to the poor compliance rate) while all other 9 studies proved the cathartic effect of castor oil; in 4 studies castor oil have similar efficacy with other preparations (such as bisacodyl or sodium phosphate); the minimum efficacy dose corresponds to 30 ml (Hsieh et al., 2000; Apisarnthanarak et al., 2009).

4.3. Clinical studies in special populations (e.g. elderly and children)

No data available.

Assessor comments: There are no studies on the potential benefits in children and adolescents. In Estonia and Latvia laxative or clearing the bowels products with castor oil are on the market which include a posology for children. However, due to the mechanism of action (anionic surfactant) and the lack of clinical data for children and adolescents , the use in children and adolescents under that 18 years of age is not recommended in the monograph.

4.4. Overall conclusions on clinical pharmacology and efficacy

The efficacy of castor oil has been evaluated in clinical trials in the treatment of constipation and for bowel cleansing before radiological investigations or colonoscopy. The use as laxative (at low dose) and cathartic at higher dose is also described in well-known pharmacological books (e.g. Goodman and Gilman's-The pharmacological basis of therapeutics, 8th ed., 1990 Katsung B.G- Basic and clinical pharmacology,8th ed., 2001; Ersparmer V. - Farmacologia medica, 1982; Sollmann T.- A manual of Pharmacology and its applications to therapeutics and toxicology, 8th ed.,1957).In Goodman and Gilman's is stated that " *in adults with empty stomach 4 ml are enough for a laxative effect while 15-60 ml have a drastic purgative effect: 1-2 evacuations with abundant semi-liquid faeces within 1-6 hours*".

Another textbook (Ersparmer V., 1982) mentioned that "*15-30 ml castor oil had a purgative effect, giving one or more semi-liquid evacuations within 2-6 hours. It is to be considered one of the most efficient, prompt and safe purgative. To be chosen to empty the bowel in case of toxic or infective enteritis, in the preparation of patients before radiological examination of the digestive tract and proctoscopy. It is contraindicated in the chronic constipation."*

Regarding the laxative effect of castor oil in constipated patients a review described two trials (one double blind positive controlled and one observational), the results supporting an well-established use indication as laxative. The short-term use the in the treatment of constipation, is approved for some

products that are on the market since 1976 and is also mentioned in pharmacological books (Goodman and Gilman, 1990; Katsung B,G, 1992).

In the monograph, a single dose of 2-5 grams is proposed. This dose is based on the results from the clinical trials: in the double blind positive controlled study 50% of the patient responded at 1.2 g/day castor oil while 2.4 g castor oil induced the same effect as 300 mg senna extract capsules. In the observational study 2-3 g/day had a laxative effect, and the recommended average doses were 3-5 g/day. The assessment report includes 14 clinical studies that investigated the efficacy of castor oil as bowel cleansing. Eleven of them were conducted in adult patients with normal bowel habits and just three included constipated patients (Strates and Hofmann, 1987; Kolts et al.,1993; Dadkhah et al., 2012); Just one study (Dadkhah et al., 2012) used a valid scale (Rome III criteria) to identify the constipated patients.

In order to assess the efficacy of castor oil the 14 clinical studies were divided in two categories: studies the treatment was combined with an enema treatment (4 studies) and studies performed without an additional enema treatment (10 studies). The results from the studies conducted without enema revealed that one study had irrelevant results (not significantly different from the control, due to the poor compliance rate) while in all other nine studies castor oil proved its cathartic effect. In 4 studies castor oil have similar efficacy with other preparations (such as bisacodyl or sodium phosphate).

HMPC is of the opinion that the clinical data are not sufficient to support a purgative indication. Posology used in the trails is too heterogeneous (from 30 ml to 80 ml, as a single or divided dose). Moreover, trial sample sizes are also too heterogeneous, in some trials less than 12 patients are included, while in other trials the groups are larger (hundreds). Also , the drop-out rate in the trails is high (more than 20%) and the compliance rate was poor (up to 32%). Furthermore, no adequate scales were used to assess the efficacy as bowel cleansing, sometimes complementary treatments were needed and alternative treatments (PEG or sodium phosphate) were more effective.

Because there are no publications that investigated the potential benefits in adolescents and children and as a general precaution taking into account the mechanism of action (anionic surfactant), the use is not recommended in children and adolescents under 18 years of age.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

Table 7: Clinical safety data from clinical trials

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Adverse reactions**	**Comments on clinical relevance of results**
Slanger et al.,1979	RPT	Senna liquid (Castor oil Single dose of X-Prep Liquid (2 1/2 oz.); Single dose of castor oil (2 oz.=56,7 g); 2 x 1 oz. X-Prep Liquid; 2 x 1 oz. castor oil; Orally Duration: single administration	100 patients (44 male 56 female 19 -86 years old, (average =60) Single dose of X-Prep Liquid (n=25) Single dose of castor oil (n=25) 2 x 1 oz. X-Prep Liquid (n=26) 2 x 1 oz. castor oil (n=24) Drop out: none	Preparing for colonoscopy	The side effects induced by the single castor oil were: nausea(2 patients/25), griping(11/25), cramps(12/25) and abdominal pain(11/25). For the divided dose the incidence was almost similar, but the severity was lower.	Castor oil was less efficient than X-Prep Liquid
Present at al., 1982	RCT, multicentric	1: water enema 2 : 4 x 1.5 g 4,4-diacetoxydiphenylpyridyl-2)-methane + 4 x 2.5 tannic acid in 2 L enema (CE) 3: 2 oz. castor oil 4: 2.5 oz. senna extract 5: 2 oz. castor oil + 2 L water enema 6: 2 oz. castor oil + 2 L CE 7: 2.5 oz senna extract+ 2L water enema 8: 2.5 oz. senna extract +2 L CE	1,800 patients For each protocol 25 patients were examined, at six different institutions Drop out: 365	Colon-cleansing regimens with single-contrast barium enema	The side effects induced by the Protocol 5(castor oil + 2 L water enema) were: nausea (29%), interference with sleep (31%), severe cramp(35%), faintness(16%), bleeding (8%)	Water enema only or castor oil only are the least effective protocols.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse reactions	Comments on clinical relevance of results
		9 bisacodyl 20 mg, orally+ 2 L water enema 10: bisacodyl 20 mg (p.o) + 2 L CE 11 : bisacodyl 20 mg (p.o) + bisacodyl 10 mg suppositories 12: magnesiun citrate +3 x 20 mg bisacodyl, p.o + 10 mg bisacodyl suppositories. Orally and rectal administration Duration: single administration				
Yang et al., 1990	RCT Duration: single administration	six protocols 1. normal saline enema, 2. castor oil with normal saline enema, 3. castor oil with soapsuds enema, 4. magnesium citrate with normal saline, 5. magnesium citrate with soapsuds enema and 6. PEG solution. Duration: single administration	247 partients age: 43 $\pm$ 15 years old 133 males 114 females Protocol 1 (n=24) Protocol 2(n=58) Protocol 3 (n=33) Protocol 4(n=40) Protocol 5(n=40) Protocol 6(n=49)	Prior to colonoscopy	Side effects as abdominal distension, pain, nausea and vomiting: were in the order of protocols: 3(88.9%), 6(79.6%), 1(75%), 5(72.5%), 2(72.4%), 4(67.5%).	Castor oil was less effective compared with PEG solution
Chen et al., 1999	RPT	Castor oil (60 mL) Magnesium citrate solution (250 mL) and bisacodyl (10 mg)	70 patients Castor oil (n = 34) Magnesium citrate + bisacodyl	Preparing for colonoscopy	The incidence of castor's oil side effects: Abdominal pain (38%) Nausea(29%) Vomiting (18%)	Magnesium citrate-bisacodyl regimen was more efficient than castor oil

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse reactions	Comments on clinical relevance of results
		Orally Duration: single administration	(n = 36)		Abdominal fullness(18%) Fainting(24%)	
Apisarnthanarak et al.,2009	RPT	Castor oil 30 ml Sodium phosphate preparation 90 ml Orally Duration: single administration	100 patients 39 males, 61 females 22-82 years old (mean = 53.0). Castor oil (n = 50) Sodium phosphate (n = 50) Drop out: 4 patients	Bowel preparation	The incidence of castor's oil side effects: Dizziness(15%) Nausea (44%) Vomiting (6%) Abdominal cramping (38%) Fatigue(32%) Fainting (6%) Palpitation(6%) Incontinence(30%)	No difference in efficacy between castor oil and sodium phosphate
Sani, et al., 2010	RPT	Castor oil(60 ml) Sena-Graph syrup (60 ml) Duration: single administration	140 patients Castor oil(n=57) Sena-Graph syrup (n=57) Drop out: 11	Bowel preparation before IVU	In castor oil group: Nausea (56.1%) Vomiting(54.4%) Abdominal pain (63.2%) Thirst(56.1%) Abdominal fullness(68.4%) Insomnia(50.8%) The incidence of diarrhea was higher in Sena-Graph group (100% vs. 91.2% for castor oil) but its severity was higher in castor oil group	Sena-Graph syrup was more efficient compared to castor oil
Dadkhah et al., 2012	RCT	Castor oil (80 ml), orally, Control Duration: single administration	186 patients 39 patients with chronic constipation 147 patients with normal bowel habits	Bowel preparation before kidney-ureter-bladder radiographies	Side effects in castor oil group: moderate or severe abdominal pain in 21 patients (23.1%), nausea in 9(9.9%) and	Patients with chronic constipation who received castor oil revealed a significantly better visualization

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse reactions	Comments on clinical relevance of results
			Castor oil (n=17 constipated; n=74 normal) Control (n=22 constipated; n=73 normal)		vomiting in 4 patients (4.4%) patients.	score.

RCT= randomised control trial; RPT= randomised positive control trial

5.2. Patient exposure

Aside from its market presence and data from clinical studies in humans, castor oil can be found also in food as a flavoring substance and/or adjuvant (21 CFR 172.510). The joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) expert committee on food additives (JECFA) has evaluated the castor oil and approved it as safe for use in food as a carrier solvent and/or release agent. FAO/WHO established an acceptable daily intake (for man) of 0 to 0.7 mg/kg body weight for castor oil. The Flavor and Extract Manufacturers Association (FEMA) has also evaluated the food-flavoring uses of castor oil and determined that it is GRAS (FEMA No. 2263). (Burdock, 2006).

5.3. Adverse events, serious adverse events and deaths

Clinical trials- see section 5.1.

Pharmacovigilance database:

In the VigiLyze database of the World Health Organization's Uppsala Monitoring Centre for the period up to August 2014, there were 23 spontaneous reports of suspected adverse drug reactions associated with the single-ingredient *castor oil.* The adverse reactions declared with the highest incidence were: nausea, abdominal pain, diarrhoea.

Case reports:

Hagenfeldt et al. (1986) reported epoxydicarboxylic aciduria (large amounts of 3,6-epoxyoctanedioic, 3,6-epoxydecanedioic and 3,6-epoxydodecanedioic acids) in a woman, possible as result from the ingestion of **castor oil (dose unknown)**.

In a case report by **Steingrub et al.** (1988), a 33-year-old pregnant female (at week 40 of gestation) ingested castor oil to induce labor. Within 60 min of ingestion, cardiopulmonary arrest occurred and was reportedly due to amniotic fluid embolism.

Market overview:

Adverse events were also mentioned from Member States. Federal Institute for Drugs and Medical devices (BfArM) reported the following adverse reactions: gastric irritation, nausea, vomiting, painful intestinal cramps and severe diarrhoea that may occur with increasing dose. In such cases dose reduction is necessary.

Chronic use (abuse) may lead to increased loss of water and electrolytes. Especially loss of potassium may occur which can cause disturbance of heart function and muscle weakness.

Hypersensitivity reactions of the skin were reported
On the basis of the available data the frequency is not assessable. So the frequency is not known.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

According to Toxnet system (http://toxnet.nlm.nih.gov), the oral use of castor oil in infants during the first 2 to 3 days of life can induce paralytic ileus and aspiration pneumonia. The same database reported severe hypoalbuminemia, diarrhea and malnutrition in a 1.5-month-old infant after daily ingestion of castor oil from the fifth day of life.

There are no studies on the potential benefits or safety in children and adolescents. Therefore, as a general precaution taking into account the mechanism of action (as anionic surfactant), the use is not recommended in children and adolescents under 18 years of age.

5.5.2. Contraindications

Castor oil is contraindicated in patients with known hypersensitivity to castor oil, intestinal obstruction and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, bile-duct diseases, severe dehydration state with water and electrolyte depletion (**Gruenwald *et al.,* 2004**)

According to WHO monograph, the use of high doses of castor oil during pregnancy and lactation is contraindicated (**WHO, 2009**).

5.5.3. Special Warnings and precautions for use

In general, if stimulant laxatives are taken for longer than a brief period, this may lead to impaired function of the intestine. The altered intestinal permeability caused by castor oil may reflect grosser morphological damage to the intestinal epithelium. The strong purgative action can cause colic as well as dehydration with electrolyte imbalance. For these reasons and because of possible reduction of the absorption of nutrients, long-term use of castor oil must be avoided (**Brunton, 1990**)

Castor oil should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

Patients taking medicinal products mentioned in chapter "interactions" have to consult a doctor before taking castor oil.

5.5.4. Drug interactions and other forms of interaction

Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products. Concomitant use with diuretics, adrenal corticosteroids and liquorice root may enhance loss of potassium. Concomitant use of antihistamines may reduce the laxative action of castor oil. The absorption of fat-soluble vitamins may be inhibited (WHO, 2009).

These interactions are are included in the product information of products that authorized in Germany.

5.5.5. Fertility, pregnancy and lactation

Castor oil has been widely used as a method of initiating labour in midwifery practice. Its role in the initiation of labour is poorly understood but this effect was studied in several trails.

Davis *et al.* (1984) investigated the use of castor oil to stimulate labor in 196 patients with premature rupture of membranes (PROM), who were between 37 and 42 weeks of gestation. Of the 196 patients, 107 (mean age=28.6 years) were dosed orally with castor oil (2 oz = 56,7 g) and 89 (mean age=27.6 years) were not. Castor oil was administered only to PROM patients who had a latency period of at least 4 h. Of the 107 patients dosed with castor oil, 80 (75%) had labour onset. Spontaneous labour occurred in 52 (58%) of the 89 control patients. This difference between patients dosed with castor oil and controls was statistically significant ($p<0.05$). The interval between castor oil administration and the onset of labor ranged from 1 to 13 h (mean=4h). Labour outcomes were also evaluated for type of delivery, incidence of oxytocin stimulation, and infant well-being. The need for cesarean sections was nearly three times greater in the control group (15.7% incidence) than in patients dosed with castor oil (5.6% incidence). This difference was found to be statistically significant ($p<0.01$).

Garry *et al.* (2000) evaluated the use of castor oil to induce labour in 52 pregnant women (mean age =24.8±6.7 years). The untreated control group consisted of 48 pregnant women (mean age=24.4 ±4.9 years). Castor oil was administered as a 60-ml dose in orange or apple juice, and its use was deemed successful only if active labour began within 24 h. Labour was defined as one or more contractions every 5 min, with cervical dilatation of 4 cm or more. Active labour was induced in 30 (57.7%) of the 52 women dosed with castor oil, compared to 2 of the 48 women in the control group ($p<.001$). The cesarean section rate for women dosed with castor oil was 19.2% (10 of 52 women), compared to 8.3% (4 of 48 controls) in the untreated control group. No relationship between dosing with castor oil, birth weight, and mode of delivery ($p=0.66$) was found.

Kelly's meta-analysis that included three trials, involving 233 women revealed that there was no evidence of the effects of castor oil for third trimester cervical ripening or induction of labour in comparison with other methods. There was no evidence of a difference between castor oil and placebo/no treatment in caesarean section rates, for the rate of instrumental delivery (RR 0.46, 95% CI 0.10 to 2.26), meconium-stained liquor (RR 0.62, 95% CI 0.23 to 1.66) or Apgar score less than seven at five minutes (**Kelly *et al.,* 2013**).

These data suggest that castor oil at high dosesn (57-60 ml) may influence the labour. These doses are at least 10 times higher than the recommended laxative dose (2,1- 5,3 ml). No data on fertility is available.

The use during lactation is not recommended, because ricinoleic acid is absorbed orally and excreted into human breast milk. According to the WHO, a purgative effect was observed in breastfed infants when the mother had used castor oil(**WHO, 2009**)

5.5.6. Overdose

Overdosage can lead to gastric irritation with nausea, vomiting, colic and severe diarrhoea, loss of electrolytes and water (**Gruenwald *et al.,* 2004**)

Treatment should be supportive with generous amount of fluid and correction of electrolytes. A specific antidote is not available.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed. Taking into account the effect of castor oil, intake of it before driving a car or operating machinery is not recommended, because the onset time of defecation may vary (2-6 hours).

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Based on the clinical safety data, and the number of and nature of side effects reported in Member States, the oral administration of castor oil can be regarded as safe. Given the history of long-term and present use in humans, also in food there are no safety concerns for the oral use of castor oil.

From clinical trials, spontaneous reports and information from the Member States the most frequently reported adverse events were: gastric irritation, nausea, vomiting, cramps and severe diarrhoea. The frequencies are not known.

The use of castor oil for a longer period may lead to morphological damage to the intestinal epithelium, this inducing impaired function of the small intestine, as dehydration with electrolyte imbalance. Especially the loss of potassium may occur which can cause disturbance of heart function and muscle weakness. Therefore long-term use of castor oil as laxative must be avoided.

The duration of use proposed for the corresponds to 1 week, which is less than the duration of the observational study (Buechi et al. 2000) but in agreement with the double blind randomised positive control trial (Buechi et al. 2000) and other European union monographs for the same therapeutic indication.

Castor oil cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate safety data and taking into account its mechanism of action, as anionic surfactant. Nonclinical and clinical data are suggesting that high doses of castor oil (57-60 ml) may influence the labour. These doses are at least 10 times higher than the recommended dose (2,1- 5,3 ml), therefore it is unlikely to observe the same effects at laxative dosage.The use during pregnancy is not recommended. The use during lactation is not recommended because ricinoleic acid is excreted into human breast milk. No data on fertility is available.

6. Overall conclusions (benefit-risk assessment)

Products containing castor oil (virgin and refined) have been registered as traditional herbal medicinal products or well-established use in some Member States. The medicinal use of castor oil has been documented in several medicinal handbooks throughout a period of at least 30 years, including at least 15 years within the EU.

Several experimental findings demonstrate that castor oil has laxative properties. Orally ingested ricinolein, the main constituents of castor oil, is hydrolyzed in the small intestine to ricinoleic acid that acts as a local irritant resulting in extensive electrolyte secretion in the small intestine by reducing net absorption of fluid and electrolytes.

Several studies in vitro and in vivo have shown that relatively high concentrations of ricinoleic acid can cause ultrastructural alterations in the villous tips of the intestinal mucosa, but the effects are reversible in all species investigated(CD-1 mice, rats, ponies).

The available clinical studies are supporting the use of castor oil as a well-established product with recognized efficacy and acceptable safety. The use as laxative, at low doses is also described in well-known pharmacological books.

The laxative effect of castor oil observed in the clinical results is in line with the well-established use indication (for short term-use in cases of constipation) of authorized products in EU.

In conclusion, based on well established use in the EU and available clinical evidence one indication is proposed under well established use:

Laxative for short-term use in cases of occasional constipation

The available clinical data is considered insufficient to support the use as a purgative.

Benefit - risk assessment

Herbal preparations with castor oil have a general positive benefit – risk balance.

The benefit of the medicinal use in the specified well established indication is adequately demonstrated.

In some Member States the use on castor oil is considered obsolete. No safety concerns could be retrieved from literature and pharmacovigilance data which justifies this classification. Moreover, products containing Castor oil product are authorized medicinal products for the proposed indication as in several EU Member States.

The use during pregnancy and lactation is not recommended, taking into account nonclinical and clinical data that are suggesting that high doses of castor oil may influence the labour.. No data on fertility is available.

Castor oil cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate efficacy and safety data.

From clinical trials, spontaneous reports and information from the Member States the most frequently reported adverse events were: gastric irritation, nausea, vomiting, cramps and severe diarrhoea. These reactions should be listed as undesirable effects in section 4.8 of the monograph. The frequencies are not known.

Adequete tests on genotoxicity and carcinogenicity for Ph Eur grade castor oil haven not been performed.

ATC code: A06 AB 05 Contact laxative

Annex

List of references