SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Izinova concentrate for oral solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This medicinal product is a concentrated sulphate-based saline solution to be further diluted in water before administration [see section 4.2]. One treatment comprises the intake of two bottles. The content of each of the two bottles is identical. Quantities of active ingredients in one and two bottles are presented below:

	1 bottle containing about 176 ml concentrate (195.375 g)	2 bottles corresponding to 2 x about 176 ml concentrate (390.750 g)
Sodium sulphate anhydrous	17.510 g	35.020 g
Magnesium sulphate heptahydrate	3.276 g	6.552 g
Potassium sulphate	3.130 g	6.260 g

The total content of electrolyte ions is as follows:

	Content in g		Content in mmol	
	1 bottle	2 bottles	1 bottle	2 bottles
Sodium*	5.684	11.367	247.1	494.2
Potassium	1.405	2.81	35.9	71.8
Magnesium	0.323	0.646	13.3	26.6
Sulphate	14.845	29.69	154.5	309.0

* derived from sodium sulphate (active ingredient) and sodium benzoate (excipient).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for oral solution.

Clear to slightly hazy solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Izinova is indicated in adults for bowel cleansing prior to any procedure requiring a clean bowel (e.g. bowel visualisation including endoscopy and radiology or surgical procedure).

Izinova is not a treatment for constipation.

4.2 Posology and method of administration

Posology

Adults

Two bottles of Izinova are needed for appropriate cleansing of the bowel. Prior to administration, the content of each bottle must be diluted in water, using the cup provided, to a total volume of approximately 0.5 litres, and must be followed by the ingestion of an additional 1 litre of water or clear liquid within 2 hours.

Authorised clear liquids are: water, tea or coffee (no milk or non-dairy creamer), fizzy (carbonated) or still (non-carbonated) soft drinks, strained fruit juices without pulp (not coloured red or purple), clear soup or soup strained to remove any solids.

In total, the volume of liquid intake required for bowel cleansing is approximately 3 litres taken orally prior to the procedure. This medicine can be taken either as a split-dose (two-day; with the first bottle taken the night before the procedure, and the second to be taken the following morning), or as a one-day oral preparation as described below (see *Method of administration*). The exact regimen and rate of ingestion of Izinova may be determined by the physician.

If allowed by the timing of the procedure, the split-dose regimen should be favoured over the one-day regimen. The one-day dose regimen is a potentially useful alternative regimen.

Method of administration

SPLIT-DOSE (TWO-DAY) REGIMEN

The day before the procedure:

Early in the evening prior to the procedure (e.g.: 6:00pm), the following instructions should be followed:

- The content of one bottle of Izinova should be poured into the cup provided in the package and should be diluted with water to the fill line (i.e.: about 0.5 litres).
- The patient should drink this diluted solution followed by two additional cups filled to the fill line with water or clear liquid (i.e.: approximately 1 litre) over the next two hours.

The day of the procedure:

On the morning of the procedure (10 to 12 hours after the evening dose), the instructions from the previous evening should be repeated:

- The content of the second bottle of Izinova should be poured into the cup provided in the package and should be diluted with water to the fill line (i.e.: about 0.5 litres).
- The patient should drink this diluted solution followed by two additional cups filled to the fill line with water or clear liquid (i.e.: approximately 1 litre) over the next two hours.

The intake of the whole diluted solution of Izinova and additional liquid (water or clear liquid) should be completed:

- In the absence of anaesthesia, at least one hour prior to the start of the procedure.
- In case of anaesthesia, usually at least 2 hours prior to the start of the procedure, in accordance with the instructions of the anaesthetist.

ONE-DAY DOSING REGIMEN (alternative dosing regimen for use depending on individual patient clinical requirement)

The evening before the procedure:

Early in the evening prior to the procedure (e.g.: 6:00pm):

- The content of one bottle of Izinova should be poured into the cup provided in the package and should be diluted with water to the fill line (about 0.5 litres).
- The patient should drink this diluted solution followed by two additional cups filled to the fill line with water or clear liquid (i.e.: approximately 1 litre) over the next two hours.

Approximately 2 hours after the start of the first dose (e.g.: 8:00pm):

- The content of the second bottle of Izinova should be poured into the cup provided in the package and diluted with water to the fill line (about 0.5 litres).
- The patient should drink this diluted solution followed by two additional cups filled to the fill line with water or clear liquid (i.e.: approximately 1 litre) over the next two hours.

The intake of the whole diluted solution of Izinova and additional liquid (water or clear liquid) should be completed:

- In the absence of anaesthesia, at least one hour prior to the start of the procedure.

- In case of anaesthesia, usually at least 2 hours prior to the start of the procedure, in accordance with the instructions of the anaesthetist.

After the procedure
In order to replace fluid lost during the preparation for the procedure, patients should be encouraged to drink a sufficient amount of fluids afterwards to maintain adequate hydration.

Dietary restrictions
The day prior to the procedure, a light breakfast may be consumed. Afterwards the patient should only have clear liquids for lunch, dinner and any other meals until the procedure is performed. Red and purple liquids, milk and alcoholic beverages should be avoided.

Special populations

Elderly population
No overall differences in safety or efficacy were observed between elderly patients and other patients during the clinical development of Izinova [see section 5.1]. Dose adjustment is not required in the elderly patients however; special precautions for use should be taken in this population as for any high-risk population [see section 4.4].

Patients with renal impairment
Insufficient data are available for this population. Dose adjustment is not required in the patients with mild to moderate renal impairment however special precautions should be taken in this population as for any high-risk population. Izinova should not be used in patients with severe renal impairment (see sections 4.3 and 4.4).

Patients with hepatic impairment
Insufficient data are available for this population. Dose adjustment is not required in the patients with hepatic impairment however special precautions should be taken in this population as for any high-risk population (see section 4.4).

Paediatric population
The safety and efficacy of Izinova in the paediatric population (i.e. patients below 18 years old) have not yet been established. No data are available (see section 5.1).

4.3 Contraindications

Izinova is contraindicated in patients with the following conditions:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Congestive heart failure

- Serious deteriorations in general health such as severe dehydration
- Acute phases of intestinal tract inflammation including Crohn's disease and ulcerative colitis
- Acute abdominal disorders subject to surgery such as acute appendicitis
- Patients likely to present with or who already have a gastrointestinal obstruction or stenosis
- Known or suspected gastrointestinal perforation
- Disorders of gastric emptying (e.g. gastroparesis, gastric stasis)
- Patients likely to present with or who already have an Ileus
- Toxic colitis or toxic megacolon
- Nausea and vomiting
- Ascites
- Severe renal insufficiency (glomerular filtration rate <30 ml/min/1.73m^2).

4.4 Special warnings and precautions for use

Electrolyte disorders and dehydration:

- Given the potential risk of severe electrolyte disorders, the benefit/risk ratio of Izinova needs to be carefully considered before initiating treatment in at-risk populations. Special attention should be given when prescribing Izinova to any patients with regard to known contraindications, and special precautions for use, including the importance of adequate hydration.
- All patients should be advised to hydrate adequately before, during and after the use of Izinova. If a patient develops significant vomiting or signs of dehydration after taking the medicine, rehydration measures should be set up to avoid the potential risks of serious complications associated with fluid and electrolyte disturbances (such as seizure and cardiac arrhythmia). In addition, performing pre-procedure laboratory tests (electrolytes, creatinine and blood urea nitrogen) should be considered. The patient should be advised to drink as much additional water or clear liquids as necessary to maintain an appropriate level of hydration.
- Dehydration could lead to functional renal failure reversible with appropriate fluids administration.

At-risk patients:

- In debilitated fragile patients, elderly patients, those with clinically significant renal, hepatic or cardiac impairment and those at risk of

electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte and renal function tests.

- Patients presenting dehydration or patients with electrolyte abnormalities should have them corrected before administration of the bowel cleansing preparation. In addition, use caution in patients with conditions, or who are using medications, that increase the risk of fluid and electrolyte disturbances (including hyponatraemia and hypokalaemia) or may increase the risk of potential complications. In this case, patients should be appropriately monitored.
- There is a theoretical risk that QT interval prolongation may occur as a result of electrolyte imbalance.

Use with caution in patients with:

- Impaired gag reflex and patients prone to regurgitation or aspiration. Such patients should be observed during administration of the bowel cleansing preparation.
- Gastrointestinal hypomotility disorders or a history of medical conditions or gastrointestinal surgery that predispose to hypomotility disorders.

Hyperuricaemia:

- Izinova can cause temporary mild to moderate elevations in uric acid [see section 4.8]. The potential for uric acid elevation should be considered before administering Izinova to patients with history of gouty manifestation or hyperuricaemia (see section 4.8).

Ischaemic colitis:

- Osmotic laxatives could cause aphtous ulcers of the colonic mucosa. Serious cases of ischaemic colitis requiring hospitalisation have been reported. Consequently, this diagnosis is to be considered in the event of abdominal with or without proctorrhagia after the administration of Izinova.

Additional information:

- Izinova is not for direct ingestion. Direct ingestion of the undiluted solution may increase the risk of nausea, vomiting, dehydration and electrolyte disturbances. Each bottle must be diluted with water and taken with additional water as recommended to ensure patient tolerance.
- This medicinal product contains 247.1 mmol (or 5.684 g) sodium per bottle. To be taken into consideration by patients on a controlled sodium diet.
- This medicine contains 35.9 mmol (or 1.405 g) potassium per bottle. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

As for any other bowel cleansing preparations:

- Use caution in patients using calcium channel blockers, diuretics, lithium treatment, or medications that might affect electrolyte levels.
- Caution is also advised when taking medicines known to prolong the QT interval.
- Diarrhoea is the expected outcome and concomitant oral medication administered within 1 to 3 hours of the start of the treatment and until the end of the cleansing process may be flushed from the gastrointestinal tract and the medication may not be absorbed properly. The therapeutic effect of regularly taken oral drugs with a narrow therapeutic index or short half-life (e.g. oral contraceptives, antiepileptic drugs, antidiabetics, antibiotics, levothyroxine, digoxin…) may be particularly affected.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with sodium, magnesium and potassium sulphates [see section 5.3].

There are no data from the use of this product in pregnant women.

Izinova is not recommended during pregnancy.

Breast-feeding

It is unknown whether Izinova is excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Izinova until 48 hours after receiving the second dose of Izinova.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

Izinova has no influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Diarrhoea is the expected outcome of the bowel cleansing preparation; therefore this occurs after Izinova ingestion. As with any intervention of this type, undesirable effects occur in the majority of patients. The most commonly reported adverse drug reactions from clinical trials and post-marketing experience are discomfort, abdominal distension, abdominal pain, nausea, and vomiting.
During clinical trials more patients reported vomiting when Izinova was given as a one-day preparation than when split-dose regimen was followed.

Tabulated summary of adverse reactions

The frequency of adverse drug reactions to Izinova is classified as follows:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), unknown (cannot be estimated from the available data).

The table below lists adverse drug reactions collected from clinical trial data, and includes events experienced by individual patients. Additionally, adverse events reported in post-marketing are included.

System Organ Class	Frequency	Adverse Drug Reaction
Immune System Disorders	Unknown (post-marketing data)	Hypersensitivity (including urticaria, pruritus, rash, erythema, dyspnoea, throat tightness)
Metabolism and nutrition disorders	Unknown (post-marketing data)	Dehydration
	Unknown (post-marketing data)	Electrolyte imbalance
Psychiatric disorders	Unknown (post-marketing data	Confusional state*
Nervous System Disorders	Uncommon	Headache, dizziness
	Unknown (post-marketing data)	Loss of consciousness*
	Unknown (post-marketing data)	Tremor*
Cardiac disorders	Unknown (post-marketing data)	Cardiac arrhythmia* Palpitations*
Gastrointestinal Disorders	Very common	Abdominal distension, abdominal pain, nausea, vomiting
	Uncommon	Anorectal discomfort, dry mouth
	Unknown (post-marketing data)	Ischemic colitis
Skin and subcutaneous tissue disorders	Unknown (post-marketing data)	Hyperhidrosis*
Musculoskeletal and connective tissue disorders	Unknown (post-marketing data)	Muscle spasms*
Renal and Urinary Disorders	Uncommon	Dysuria
General Disorders and Administration Site Conditions	Very common	Discomfort
	Uncommon	Chills
	Unknown (post-marketing data)	Asthenia*
Investigations	Uncommon	Aspartate aminotransferase increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood phosphorus increased, hyperbilirubinaemia, blood chemistry disturbances including hyponatraemia, hypokalaemia, hypocalcaemia ***and*** hyperuricaemia

*Clinical consequences of dehydration and/or electrolyte imbalance

Additional information on special populations

Temporary elevations in uric acid have been observed during clinical trials. For patients with history of gouty manifestation or with hyperuricaemia, see section 4.4.

No overall differences in safety were observed between the elderly population and the other patients during the clinical development of Izinova [see section 5.1]. However special precautions for use should be taken in elderly patients as for any high-risk population [see section 4.4].

For patients with renal or hepatic impairment, see sections 4.3 and 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In case of overdose or misuse (e.g.: non-dilution of the preparation and/or insufficient water intake), nausea, vomiting, diarrhoea and electrolyte disturbances would be expected. Conservative measures are usually sufficient; oral rehydration therapy should be given. In the rare event of overdose triggering a severe metabolic disturbance, intravenous rehydration should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: osmotically acting laxative.

ATC code: A06AD10 (mineral salts in combination).

Mechanism of action

Izinova is an osmotic laxative. Its mechanism of action primarily relies on the limited and saturable sulphate active transport process. Saturating the gastrointestinal transport mechanism leaves sulphate in the bowel. The osmotic effect of unabsorbed sulphate causes water to be retained in the bowel and leads to bowel cleansing.

Pharmacodynamic effects

The osmotic effect of the unabsorbed ions, when ingested with a large volume of water, produces a copious watery diarrhoea. In clinical trials, the mean time until a clear diarrhoea was about 6.3 hours when the doses were separated by 12 hours and about 2.8 hours when they were consumed 1 hour apart.

Clinical efficacy and safety

Clinical efficacy of Izinova was demonstrated in two randomised, actively-controlled,
multi-centre, investigator-blinded phase III pivotal clinical trials.
The primary efficacy analysis was based on the cleansing success or failure rate
determined for each subject. For statistical analysis, a bowel cleansing graded either
'good' or 'excellent' was considered 'successful' while those graded either 'poor' or
'fair' were considered 'failures'. Those who did not undergo colonoscopy were
considered treatment failures.

Results of the studies, which compared Izinova to a 2-litre polyethylene glycol (PEG)
plus electrolytes solution, respectively administrated in split-dose regimen (379
patients randomised, 356 patients in the per protocol (PP) population) and in one-day
dosing regimen (408 patients randomised, 364 patients in the PP population), show
the non-inferiority of Izinova compared to the 2-litre PEG-based product in both
dosing regimen conditions regarding primary endpoint: i.e. the rate of bowel
cleansing graded either excellent or good of Izinova and the 2-litre PEG-based
product was similar (results of PP population):

- for the split-dose regimen : 97.2% and 96.1%, for Izinova and the 2-litre PEG-based product respectively [with a CI95% : -2.7 to 4.8 within the predefined margin of 15%] ;
- for the one-day regimen : 84% versus 82.9%, for Izinova and the 2-litre PEG-based product respectively [with a CI95% ; -6.5 to 8.8 within the predefined margin of 15%.

Adverse events were predominantly gastrointestinal as expected for any bowel
cleansing agent; abdominal distension, abdominal pain nausea and vomiting were the
most frequent symptoms reported.

<u>Paediatric population</u>

The European Medicines Agency has waived the obligation to submit the results of
studies with Izinova in infants from birth to 6 months old and has deferred the

obligation to submit the results of studies with the medicine in the rest of the paediatric population, i.e.: in the sub-sets from 6 months to 17 years old, inclusive

[see section 4.2 for information on paediatric use].

5.2 Pharmacokinetic properties

Sulphate absorption is a limited and saturable active transport process; absorbed sulphate is excreted primarily via the kidneys. After administration of a clinical formulation with the same sulphate content as Izinova in six healthy volunteers, according to the split-dose regiment, i.e. two doses separated by 12 hours, the maximum serum concentration of sulphate was observed approximately 16 hours after the first half dose and 5 hours after the second dose [C max: 499.50 µmol/l (CV: 33.03%) in comparison to baseline values of 141 – 467 µmol/l mean 335 µmol/l (CV: 34.40%)]. Serum concentration then declined with a half-life of 8.5 hours (CV: 53.76%). Faecal excretion was the primary route of sulphate elimination (about 70% of the amount administered).

The systemic exposure (AUC and C_{max}) to sulphate after Izinova was also compared between healthy volunteers, six patients with moderate renal impairment (creatinine clearance of 30 to 49 ml/min) and six patients with mild-moderate hepatic impairment (Child-Pugh grades A (N=5) and B (N=1)), respectively. Renal impairment resulted in a decrease in the amount of sulphate excreted into urine. Consequently, the mean AUC and C_{max} values were about 50% higher compared to healthy subjects. Systemic exposure to sulphate was not affected by hepatic impairment. The serum sulphate concentrations returned to baseline by Day 6 after Izinova administration in all three groups investigated. In this study Izinova use did not lead to clinically significant hypersulphataemia in patients with hepatic or renal impairment.

5.3 Preclinical safety data

No reproductive toxicity studies or studies to evaluate the mutagenic or carcinogenic potential have been performed with the combination of sodium, magnesium and potassium sulphate salts

Limited non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity.

The sodium, magnesium and potassium sulphate salts are unlikely to represent a risk for the environment and no specific precautionary and safety measures have to be taken for the storage and administration of the drug product containing these drug substances. For special precautions for disposal, see Section 6.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)

Citric acid, anhydrous

Malic acid

Sucralose

Purified water

Fruit cocktail flavour.

Composition of the fruit cocktail flavour:

Natural and synthetic flavouring substances, propylene glycol E1520, ethyl alcohol, acetic acid and benzoic acid E210.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After first opening of the bottle and/or diluting in water, the solution should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from light.

For storage conditions after first opening/dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

About 176 ml concentrate in a light amber bottle (polyethylene terephtalate) with a child-resistant closure (high density polyethylene).

One cup (polypropylene) with a fill line defining a volume of about half a litre is provided with the bottles, to be used as a dilution and administration device.

Pack size of two bottles and one cup available as:

1 pack of two bottles and one cup

24 x 1 pack of two bottles and one cup

6 x 24 (=144) x 1 pack of two bottles and one cup

14 x 24 (=336) x 1 pack of two bottles and one cup

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product must be diluted before use with the amount of water stated in the method of administration [see section 4.2].

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

MAYOLY
PHARMA
FRANCE
3 Place
Renault
92500
Rueil-
Malmaiso
n
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 51419/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/03/2013

10 DATE OF REVISION OF THE TEXT

15/07/2025