

אוגוסט 2015

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכונים בעלונים לרופא ולצרכן של התכשירים:

פרפלגן 10 מ"ג /מ"ל

Perfalgan 10mg/ml

חומר פעיל: Paracetamol 10mg/ml

התוויה כפי שאושרה בתעודת הרישום:

Perfalgan is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

בהודעה זו מצוינים רק הסעיפים בהם נעשה שינוי אשר מהווה החמרה או שינוי מהותי.

טקסט שהתווסף מסומן **באדום ובקו תחתון**. טקסט שהוסר מסומן **בקו אמצעי**.

למידע מלא יש לעיין בעלון לרופא העדכני כפי שאושר ע"י משרד הבריאות הישראלי.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל

הרישום בריסטול-מאירס סקוויב (ישראל) בע"מ, ת.ד. 3361, קרית אריה, פתח תקווה 4951448 או בטלפון

03-5231021.

בכבוד רב,

טליה בן דוד,

רוקחת ממונה

4. CLINICAL PARTICULARS

...

4.2 Posology and method of administration

Intravenous route.

The 100 ml vial is restricted to adults, adolescents and children weighing more than 33 kg.

The 50 ml vial is adapted ~~restricted~~ to term newborn infants, infants, toddlers and children weighing less than 33 kg.

Severe renal insufficiency:

It is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤ 30 ml/min), to reduce the dose and increase the minimum interval between each administration to 6 hours (See section 5.2).

...

Method of administration:

...

Patients weighing ≤ 10 kg:

- The glass vial of Perfalgan should not be hung as an infusion due to the small volume of the medicinal product to be administered in this population.
- The volume to be administered should be withdrawn from the vial and could be administered undiluted or diluted (from one to nine volumes diluent) in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume Perfalgan into nine volumes diluent) and administered in over 15 minute.
Use the diluted solution within the hour following its preparation (infusion time included).
- A 5 or 10 ml syringe should be used to measure the dose as appropriate for the weight of the child and the desired volume. However, this should never exceed 7.5ml per dose.
- The user should be referred to the product information for dosing guidelines.

~~Text for the 50ml and 100ml vials:~~

To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.

~~Text for the 50ml and 100ml vials:~~

As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.

Text for the 50ml vial:

Perfalgan of 50ml vial can also be diluted in a 0.9% sodium chloride solution or 5% glucose solution ~~up to one tenth~~ (from one volume Perfalgan into to nine volumes diluent). In this case, use the diluted solution within the hour following its preparation (infusion time included).

4.3 Contraindications

PERFALGAN is contraindicated:

- In patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.
- In cases of severe hepatocellular insufficiency or decompensated active liver disease-

4.4 Special warnings and precautions for use

Warnings

...

In order to avoid the risk of overdose, check that other medicines (including prescription and nonprescription) administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entails risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of drug administration with a peak seen usually after 4 - 6 days. Treatment with antidote should be given as soon as possible (See section 4.9).

Paracetamol can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity

This medicinal product contains less than 1 mmol sodium (23mg) per 100ml of Perfalgan, i.e. essentially "sodium free".

Text for the 50ml and 100ml vials:

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see section 4.2).

Precautions for use

Paracetamol should be used with caution in cases of:

- Hepatocellular insufficiency-
- Severe renal insufficiency (~~creatinine clearance ≤ 30 mL/min~~) (see sections 4.2 and 5.2)
- Glucose-6-phosphate dehydrogenase deficiency (may lead to haemolytic anemia)
- Chronic alcoholism excessive alcohol intake (3 or more alcoholic drinks every day)-
- Anorexia, bulimia or cachexia
- Chronic malnutrition (low reserves of hepatic glutathione)
- Dehydration, hypovolemia-

4.5 Interaction with other medicinal products and other forms of interaction

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid
- Phenytoin administered concomitantly may result in decreased paracetamol effectiveness and an increased risk of hepatotoxicity. Patients receiving phenytoin therapy should avoid large and/or chronic doses of paracetamol. Patients should be monitored for evidence of hepatotoxicity.
- Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol.
- Caution should be paid to the concomitant intake of enzyme-inducing substances (see section 4.9).

- Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.

...

4.8 Undesirable effects

As all paracetamol products, adverse drug reactions are rare ($>1/10000$, $<1/1000$) or very rare ($<1/10000$), they are described below:

Organ system	Rare $>1/10000$, $<1/1000$	Very rare $<1/10000$	<u>Isolated reports²</u>
General	Malaise	Hypersensitivity reaction	
Cardiovascular	Hypotension	<u>Shock²</u>	
Liver	Increased levels of hepatic transaminases		
<u>Blood and the lymphatic system disorders²</u> Platelet/blood	<u>Agranulocytosis, neutropenia²</u>	<u>Leucopenia</u> Thrombocytopenia <u>Leucopenia,</u> <u>Neutropenia.</u>	
<u>Neurological²</u>		<u>Neurological disorders²</u>	<u>Coma²</u>
<u>Renal/Genitourinary²</u>		<u>Acute renal failure²</u>	
<u>Skin and subcutaneous tissue disorders²</u>	<u>Macular rash, injection site reaction²</u>	<u>Maculo-papular rash, pemphigoid reaction, pustular rash²</u>	<u>Lyell Syndrome²</u>

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment. ~~Cases of erythema, flushing, pruritus and tachycardia have been reported.~~

Post Market Adverse Effects for Propacetamol/Paracetamol²

The following adverse events have also been reported during postmarketing surveillance, but incidence rate (frequency) is not known.

<u>Organ System</u>	<u>Adverse Event</u>
<u>Blood and the lymphatic system disorders</u>	<u>- Thrombocytopenia</u>
<u>Cardiac disorders</u>	<u>- Tachycardia</u>
<u>Gastrointestinal disorders</u>	<u>Nausea</u> <u>Vomiting</u>
<u>General disorders and administration site conditions</u>	<u>- Administration site reaction</u>
<u>Hepatobiliary disorders</u>	<u>Fulminant hepatitis</u> <u>Hepatic necrosis</u> <u>Hepatic failure</u> <u>Hepatic enzymes increased</u>
<u>Immune system disorders</u>	<u>Angioneurotic (Quincke's) edema</u> <u>Anaphylactic shock</u> <u>Anaphylaxis</u> <u>Hypersensitivity reactions (ranging from simple skin rash or urticaria to anaphylactic shock) have been reported and require the discontinuation of treatment</u>

Skin and subcutaneous tissue disorders

Erythema

Flushing

Pruritus

Rash

Urticaria

Acute generalised exanthematous pustulosis

Toxic epidermal necrolysis

Stevens-Johnson syndrome

...

5. PHARMACOLOGICAL PROPERTIES

...

5.2 Pharmacokinetic properties

...

Renal insufficiency

In cases of severe renal impairment (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with severe renal impairment (see section 4.2), ~~creatinine clearance \leq 30 mL/min~~, to increase the minimum interval between each administration to 6 hours (see section 4.2. Posology and method of administration).

Elderly subjects

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of PERFALGAN in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

The effects of paracetamol in the diet of rats and mice was evaluated at 0, 600, 3000, and 6000 PPM for 2 years. Paracetamol was found to be noncarcinogenic in male rats as well as in male and female

mice. Equivocal evidence of carcinogenic activity was noted for female rats based on an increased incidence of mononuclear cell leukemia.

A comparative review of the literature on paracetamol genotoxicity and carcinogenicity showed that genotoxic effects of paracetamol appear only at dosages above the recommended range resulting in severe toxic effects including pronounced liver and bone marrow toxicity. The threshold level for genotoxicity is not reached at therapeutic dosages of paracetamol.

...

6. PHARMACEUTICAL PARTICULARS

...

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

~~Text for the 50ml and 100ml vials:~~

50 ml and 100 ml Type II clear glass vial with bromobutyl stopper and ~~a~~an aluminium/plastic Flip-Off cap.

Pack size: pack of 12 vials.

6.6 Special precautions for disposal <and other handling>

~~Text for the 50ml and 100ml vials:~~

Use a 0.8 mm needle and vertically perforate the stopper at the spot specifically indicated.

...

8. LICENSE HOLDER

Bristol-Myers Squibb (Israel) Ltd., 18 Aharon Bart ~~22 Hamelacha St.,~~ Petah Tikva ~~Rosh Ha'ayin.~~