Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dolflash 500 mg orodispersible tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet cotains 500 mg paracetamol (as coated paracetamol cystals)

Excipients: each tablet also includes 40 mg aspartame (E951).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

White, round, bi-convex tablet with central concave depression with a characteristic odour of blackcurrant.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment for mild to moderate pain and/or fever.

4.2 Posology and method of administration

Posology
This medicinal product is for ADULT USE ONLY**.**

The maximum recommended posology is 3000mg of paracetamol per day, corresponding to 6 tablets daily. The usual posology is 1 tablet of 500mg, to be repeated if necessary after a minimum of 4 hours. In the event of intense pain or intense fever, 2 tablets of 500mg, to be repeated if necessary after a minimum interval of 4 hours.
Do not exceed 6 tablets of 500mg over a period of 24 hours.

*Maximum recommended posology***:** The total dose of paracetamol should not exceed 3g daily for adults *(See Section 4.9, Overdose).*

Frequency of administration
In adults, administration should take place at intervals of a minimum of four hours.

Renal insufficiency
In the case of severe renal insufficiency the minimum interval between 2 administrations should be 8 hours.

Method of Administration
Oral route.
The tablet should be sucked but not chewed. The tablet may also be dispersed in a half glass of water.

4.3 Contraindications

- Hypersensitivity to paracetamol or to any of the excipients.
- Phenylketonuria (due to the presence of aspartame).
- Severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Warnings
Do not exceed the stated dose.
Prolonged use of this product, except under medical supervision, may be harmful.
This product should only be used when clearly necessary.

Doses higher than recommended entail risk for very serious liver damage. Treatment with antidote should be given as soon as possible. See section 4.9.

To avoid the risk of overdose, patients should be advised not to take other paracetamol-containing product concurrently.
This medicinal product contains aspartame, a source of phenylalanin equivalent to 0.2 mg per tablet, and is therefore contraindicated for people with phenylketonuria *(see section 4.3, Contraindications).*

Precautions for Use
Paracetamol should be used with caution in cases of:

- Adults weighing less than 50 kg
- Mild to moderate hepatocellular insufficiency (comment : acetaminophen is contra indicated in cases of severe hepatocellular insufficiency)
- Chronic alcoholism
- Chronic malnutrition (low reserves of hepatic gluthatione)
- Dehydration
- Severe renal insufficiency (creatinine clearance ≤ 10 mL/min *(see section 4.2, Posology and Administration)*

In the case of high fever, or signs of secondary infection or persistance of symptoms beyond 3 days, a reevaluation of treatment should be made.

During long-term, high dose off label treatment with analgesic drugs, headaches can occur which must not be treated with higher doses of the medicinal product. In general the habitual use of analgesics, especially the combination of different analgesic drug substances, can lead to lasting renal lesions with the risk of renal failure (analgesic nephropathy). If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of ‘Medication Overuse Headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 glucuronid acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.
- Salicylamide may prolong the elimination t1/2 of paracetamol.
- Caution should be paid to the concomitant intake of enzyme-inducing substances (such as carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort, etc.) or potentially hepatotoxic substances *(see section 4.9, Overdose)*.
- Metoclopramide and domperidone : accelerate absorption of paracetamol.
- Cholestyramine : reduces absorption of paracetamol.

- 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 done during the duration of the combination and after its discontinuation.

Paraclinical Test Interaction
The administration of paracetamol can affect the assay of uric acid for tests carried out by the phosphotungstic acid method, and also the assay of glycemia carried out by the glucose oxydase-peroxydase method.

4.6 Fertility, pregnancy and lactation

Pregnancy
Epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the fetus / newborn infant. Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk. Reproductive studies with the oral route did not show any malformation or foetotoxic effects.
Consequently under normal conditions of use, paracetamol can be use throughout the duration of pregnancy, after a benefit-risk assessment.
During pregnancy, paracetamol should not be taken for longs periods, at high doses or in combination with other medicinal products, as safety of use in such cases is not established.

Lactation
After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Therapeutic doses of this medicinal product may be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Organ System	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000), not known (cannot be estimated from the available data)**
Hepatobiliary disorders	- increased levels of hepatic transaminases	
Immune system disorders		- hypersensitivity reaction (from simple skin rash or urticaria to anaphylactic shock requiring discontinuation of the treatment)
Blood and lymphatic system disorders		- thrombopenia, leucopenia, neutropenia (isolated reports)

4.9 Overdose

There is a risk of liver injury (including fulminant hepatitis, hepatitic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain.
Overdose, 7.5 g or more of paracetamol in a single administration in adults or 140 mg/kg of body weight in a single administration in children, causes liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death.

Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubine are observed together with increased prothrombin time that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after 2 days, and reach a maximum after 4 to 6 days.
Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

Emergency Procedure
- immediate transfer to hospital, even if there are no significant early symptoms
- blood sampling to determine initial paracetamol plasma concentration
- gastric lavage
- IV (or oral if possible) administration of the antidote N-acetylcysteine if possible *before* the 10th hour post-ingestion. N-acetylcysteine can, however, give some degree of protection even after 10 hours, and up to 48 hours, but in these cases prolonged treatment is given.
- symptomatic treatment should be implemented.
- methionine by oral route could be used as an alternative to N-acetylcysteine provided that, it is administered as soon as possible after overdose and in all cases within 10 hours of the overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : analgesics and antipyretics, anilides
ATC-code : N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

5.2 Pharmacokinetic properties

Absorption
The absorption of paracetamol by the oral route is complete and rapid. Maximal plasma concentrations are reached 30 to 60 minutes after ingestion.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in the blood, the saliva and the plasma; protein binding is low.

Metabolism
Paracetamol is metabolized mainly in the liver following 2 major pathways: glucuronic acid and sulphuric acid conjugates. This latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalyzed by Cytochrome P 450 (CYP2E1), results in the formation of an intermediary reagent, N-acetyl-p-benzoquinoneimine, which, under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination
Elimination is essentially through the urine. 90% of the ingested dose is eliminated by the kidneys in 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.
The elimination half-life is about 2 hours.

Renal insufficiency
In case of severe renal insufficiency (creatinine clearance less than 10 ml/min), the elimination of paracetamol and its metabolites is delayed.

Elderly subject: Conjugation capacity is not modified.

5.3 Preclinical safety data

In animal experiments regarding acute, subchronic and chronic toxicity of paracetamol in rats and mice, gastro-intestinal lesions, blood count changes, degeneration of liver and renal parenchyma, even necroses were observed. The causes for these changes are attributed to the mechanism of action on the one hand and on the other to the metabolism of paracetamol. The metabolites presumed to yield the toxic effects and the corresponding changes in organs have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. In case of subtoxic doses, signs of intoxication can occur after a 3-week intake.Therefore, paracetamol should not be taken over a long period of time and not at higher doses.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic, i.e. non-toxic doses.

Long-term studies in rats and mice yielded no evidence on relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol passes through the placenta.
Animal studies and experience in humans to date yield no evidence on reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Coated paracetamol crystals:
Basis butylated methacrylate copolymer
Polyacrylate dispersion 30 per cent
Hydrophobic colloidal silica

Tablet matrix
Mannitol (granulated powder)
Crospovidone
Aspartame (E951)
Blackcurrant flavouring
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Thermoformed blister (Polyamide/PVC/Aluminium): 4 years.
Thermo-set strips (Aluminium/Polyethylene): 3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Thermoformed blister (Polyamide/PVC/Aluminium): Pack sizes of 2, 4, 6, 12, 16 or 20 tablets
or
thermo-set strips (Aluminium/Polyethylene): Pack sizes of 2, 4, 6, 12 or 16 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
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92213 Saint-Cloud cedex
France

8 MARKETING AUTHORISATION NUMBER

PA 0549/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 March 2003

Date of last renewal: 22 May 2008

10 DATE OF REVISION OF THE TEXT

September 2009